Clinical Application of Peptide Growth Factors First Identified in Breastmilk

The presence of growth factors in breastmilk and investigations leading to their identification has been described in these columns. Since then developments in molecular biology and recombinant technology including genetics have helped to elucidate the structure of several growth factors, and a few have become available in sizeable amounts. These provide novel treatment options for a variety of conditions.

The epidermal growth factor (EGF) group makes up a major proportion of all peptide growth factors. Members of this group share the common property of binding to the EGF receptor. They include EGF itself, transforming growth factor α (TGF-α), the mammary derived growth factor II (MDGF-II), and human milk growth factor-III which might be the same as EGF. Most of the EGF family peptides are trophic to the gut and stimulate cell proliferation.

EGF occurs in human colostrums (200 µg/l) and milk 30–50 µg/l) as well as in several other mammalian milks, but is not found in significant amounts in cow’s milk. It has been shown that the gastric juice of pre-term infants does not deactivate milk-borne EGF under control conditions, but it is susceptible to proteolytic digestion unless in the presence of food protein. Studies in laboratory animals have shown that EGF serves to increase mucosal growth and functional adaptation following intestinal resection, diarrhoea, total parenteral nutrition, and ulcerative conditions. There has been one case report of continuous intravenous infusion of EGF to an infant with necrotizing enterocolitis resulting in recovery with restoration of gut histology. In a randomized double-blind clinical trial 12 adult subjects with mild to moderate left-sided ulcerative colitis were administered a daily enema of 5 µg of EGF in 100 ml of an inert carrier, and a control group of 12 subjects received daily enemas with carrier alone for 14 days. All subjects also received 1.2 g of oral mesalazine per day. All subjects were assessed clinically at 0, 2, 4, and 12 weeks and by sigmoidoscopy and biopsy at 0, 2, and 4 weeks. After 2 weeks 10 of the 12 patients (83 per cent) given EGF enemas were in remission as compared with one of the 12 (8 per cent) in the control group (p < 0.001). EGF may well be beneficial for infants with the short bowel syndrome following intestinal resection for vascular insufficiency, or after repeated surgery for inflammatory bowel disease. These conditions present a major challenge, and current therapeutic options such as long-term parenteral feeding or small bowel transplantation are associated with a high risk of mortality. Colostrum supplementation may be of particular value in young children with these problems since gut growth and adaptation is still taking place in them.

TGF-α occurs in much lower concentrations (2.2–7.2 µg/l) in humancolostrum and milk. It is produced within the mucosa throughout the gastrointestinal tract. Up-regulation of TGF-α expression has been shown to occur at sites of injury in the gastrointestinal mucosa as well as in the liver following partial hepatectomy indicating a role for TGF-α in mucosal growth and repair. In the healthy subject the main physiological role of TGF-α is to maintain mucosal integrity and normal epithelial function.

Insulin-like growth factors I and II (IGF-I and IGF-II) are both expressed in relatively large amounts in the developing foetal stomach and small intestine reaching a maximum soon after birth. Because of the known trophic effects of IGF-I and -II a number of candidate bowel disorders have been identified for clinical trials. For example, in children with inflammatory bowel disease IGF-I and -II levels are depressed during the acute stage and improve with remission. This observation indicates a role for the IGFs axis (consisting of the two IGFs and six IGF binding proteins) in inflammatory bowel disease. Milk and colostrum derived formulations containing IGF-I are being developed for use as adjunctive treatment and are candidates for future clinical trials.

Lactoferrin was identified decades ago as an iron binding glycoprotein present in human colostrums at a concentration of around 7 g/l, and at a lower concentration of about 1 g/l in milk. Lactoferrin has multiple effects. It is bactericidal to Gram-negative bacteria by causing damage to the outer membrane of the bacteria, and also performs immunoregulatory functions by decreasing the release of interleukins-1 and -2 (IL-1 and IL-2), and TNF-α, as well as enhancing monocyte and natural killer cell cytotoxicity. Lactoferrin binds with high affinity to the toxic lipopolysaccharide moiety of the endotoxins released by Gram-negative bacteria. Lactoferrin has been shown to stimulate the growth of various cell lines in vitro including fibroblasts and intestinal epithelial cells suggesting that its presence in milk may be important for regulating gut growth in newborns. Lactoferrin is being proposed as a useful adjunct in the treatment for eradication of Helicobacter pylori.

Colonystimulating growth factor is currently being used for stimulating bone marrow recovery after cancer chemotherapy and is now an integral part of the prevention of potentially life threatening febrile neutropenia in patients being treated for
malignancy. It has recently been approved by the US Food and Drug Administration for the purpose. Other therapeutic uses of the colony stimulating factor are under consideration. In a few clinical trials administration of colony-stimulating factor in neonatal sepsis has resulted in reduced morbidity and mortality. Further larger trials are needed to verify this claim and to properly establish its place as an adjunct in the treatment of neonatal sepsis.13

Large scale production of several of the growth factors using recombinant technology can be anticipated especially when innovative therapeutic regimens are developed for disorders that have hitherto been intractable. For resource-poor countries the cost of the new products may well become unaffordable. Administration of colostrum and breastmilk derived preparations by mouth is an attractive therapeutic option for such countries. The added advantage of this approach may well be that colostrum and milk contain different growth factors in a formulation that we know provides protection against proteolytic digestion.

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References