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Can We Protect the Gut in Critical Illness: The Role of Growth Factors and Other Novel Approaches

Jessica A. Dominguez, PhD[a] and **Craig M. Coopersmith, MD**[b]

[a] Assistant Professor of Anesthesiology, University of Colorado Denver School of Medicine, Aurora, Colorado

[b] Professor of Surgery, Emory University School of Medicine, Atlanta, Georgia

Synopsis

The intestine plays a central role in the pathophysiology of critical illness and is frequently called the "motor" of the systemic inflammatory response. Perturbations to the intestinal barrier can lead to distant organ damage and multiple organ failure. Therefore, identifying ways to preserve intestinal integrity may be of paramount importance. Growth factors and other peptides have emerged as potential tools for modulation of intestinal inflammation and repair due to their roles in cellular proliferation, differentiation, migration, and survival. In this review, we will examine the involvement of growth factors and other peptides in intestinal epithelial repair during critical illness and their potential use as therapeutic targets.

Keywords

critical illness; intestine; growth factors

Introduction

For more than two decades, the gut has been hypothesized to be the "motor" of the systemic inflammatory response syndrome. As critical care research has evolved, numerous studies have defined how the gut plays a role in the origin and propagation of critical illness. During shock, intestinal hypoperfusion followed by reperfusion leads to production of proinflammatory mediators that can amplify the systemic inflammatory response[1]. Interactions between host and bacterial pathogens in the intestine contribute to gut-derived sepsis[2]. Intestinal permeability in critical illness, as a result of compromised epithelial tight junctions, leads to persistent activation of systemic inflammation[3–5]. Toxic gut-derived substances enter the mesenteric lymph leading to lung damage, and distant organ injury can be prevented by ligating the mesenteric lymph duct in hemorrhagic shock[6]. Intestinal epithelial apoptosis is elevated following sepsis, and prevention of sepsis-induced intestinal

[a]Corresponding author for proof and reprints: Jessica A. Dominguez, PhD, Department of Anesthesiology, University of Colorado Denver School of Medicine, 12700 E. 19th Avenue, Campus Box 8602, Aurora, CO 80045, Phone: (303) 724-4398, Fax: (303) 724-2936, Jessica.dominguez@ucdenver.edu.
Co-author: Craig M. Coopersmith, MD, 101 Woodruff Circle, Suite WMB 5101, Atlanta, GA 30322, Phone: (404) 727-4273, Fax: (404) 727-3660, Cmcoop3@emory.edu

apoptosis by overexpression of the anti-apoptotic protein Bcl-2 improves survival in multiple animal models of sepsis[7,8].

Since perturbations to the intestinal epithelium can cause distant organ damage and development of multiple organ dysfunction syndrome, identifying ways to preserve intestinal integrity may be of paramount importance in the treatment of critical illness. Growth factors have emerged as potential tools for modulation of intestinal inflammation and repair, playing important roles in cellular proliferation, differentiation, migration, and survival. In this review, we will examine the involvement of growth factors and other peptides in intestinal mucosal repair during critical illness and their potential use as therapeutic targets.

Mucosal repair in the gastrointestinal tract

The mucosal lining of the gastrointestinal tract represents the largest body surface in contact with the outside world (approximately 300 m^2, roughly the area of a tennis court). The intestinal epithelium consists of a single layer of columnar epithelial cells that are constantly renewed from multipotent stem cells originating in the crypts of Lieberkühn. These stem cells give rise to four major epithelial lineages: absorptive enterocytes, goblet cells, enteroendocrine cells, and Paneth cells[9]. Over the course of a three to five day lifespan, enterocytes, goblet cells, and enteroendocrine cells migrate upwards along the crypt-villus axis where they differentiate and ultimately die of apoptosis or are exfoliated whole into the lumen[10]. In contrast, Paneth cells migrate downward over the course of five to eight days to the crypt base where they reside for approximately three weeks. Each epithelial cell is in intimate contact with its neighbors, and the integrity of the epithelium is maintained by apical junctional complexes[11]. Tight junctions are the most apical components of the complex and create a dynamic barrier to the paracellular movement of water, solutes, and immune cells[12,13].

While minor breaches in epithelial integrity occur daily due to mechanical strain associated with intestinal motility and physiologic digestive trauma, more extensive disruption of epithelial continuity can result from bacterial invasion, chemical injury, or tissue destruction due to ischemic, septic, and inflammatory enteropathies[14]. Rapid resealing of the intestinal barrier is essential to prevent systemic penetration of toxins, immunogens, and other factors that can lead to activation of the systemic inflammatory response. The gastrointestinal tract utilizes at least three distinct mechanisms to re-establish epithelial continuity (Figure 1)[15,16]. Within minutes after injury, epithelial cells bordering the zone of injury migrate into the wound to cover the denuded area. During this process, termed epithelial restitution, epithelial cells adjacent to the injury undergo a striking change in cell shape and phenotype. Instead of their normal columnar shape, the cells flatten and adopt a squamoid appearance, followed by extension of lammelipodia. In addition, the cells undergo brush border and junctional disassembly and become polarized along the leading-trailing edge axis. After the wound is sealed, the cells reorganize their cytoskeleton and redifferentiate into mature enterocytes. Epithelial cell proliferation is also stimulated in order to restore the functional capacity of the mucosa. Finally, undifferentiated epithelial cells undergo maturation and differentiation to maintain normal mucosal epithelial function. It is important to note that when an epithelial defect is large, stimulation of cell proliferation is crucial for restoration of normal mucosal architecture. If the lesion is deep or penetrating, additional repair mechanisms are required, such as angiogenesis and deposition of extracellular matrix components to form granulation tissue.

Regulation of intestinal epithelial repair by growth factors

Numerous growth factors regulate the process of epithelial repair (Figure 2)[14,17]. Growth factors control a wide variety of activities, including stimulation of proliferation and migration, cell differentiation, acceleration of angiogenesis and extracellular matrix remodeling, as well as promotion of epithelial mucosal repair[14,17]. These factors can either be derived from the luminal environment as the result of intrinsic secretions from epithelial cells, or they can be produced by a wide variety of mucosal and submucosal cells[14]. Myofibroblasts beneath a mucosal injury secrete hepatocyte growth factor (HGF) and keratinocyte growth factor (KGF), both of which stimulate migration and proliferation of epithelial cells[14]. Neutrophils also release HGF[18]. Platelets also release growth factors in response to tissue injury, including epidermal growth factor (EGF)[19], insulin-like growth factor (IGF-I)[20], and HGF [21]. These growth factors interact predominantly with receptors on the basolateral membrane of epithelial cells. In contrast, other growth factors including intestinal trefoil factor (ITF) and glucagon-like peptide-2 (GLP-2) are secreted into the lumen and act primarily at the apical surface of epithelial cells. Of note, EGF can also be secreted into the lumen and act on the apical surface. While a complete understanding of the complex interrelationships and redundancy of growth factors in epithelial repair remains to be determined, multiple studies have shed light on how these peptides protect the intestine during injury.

Epidermal Growth Factor

EGF is a potent 53 amino acid cytoprotective peptide that exhibits trophic and healing effects on the intestinal mucosa[22,23]. As a mitogen, EGF is involved with the regulation of cellular proliferation, survival, and migration. Under basal conditions, the EGF signaling pathway is crucial for intestinal epithelial proliferation and cell survival[24]. EGF receptor (EGF-R) deficient mice die early in postnatal life and exhibit severe defects in intestinal morphology, including fewer and shorter villi[25]. Activation of EGF-R following binding of EGF in the intestine can lead to increased blood flow[26], increased cell survival[27,28], decreased inflammation[29], and improved barrier function[30,31].

There is significantly more preclinical data on the use of EGF in adult critical illness than other growth factors. Circulating EGF levels are decreased while intestinal EGF and EGF-R levels are increased following cecal ligation and puncture (CLP), a preclinical model of peritonitis-induced sepsis[32]. Animals subjected to CLP have increased sepsis-induced apoptosis, and this is associated with increased expression of Bid, FADD and p21. Apoptosis is normalized to sham levels in mice treated with exogenous EGF after the onset of sepsis, as are the levels of Bid, FADD and p21. Septic mice also have decreased intestinal proliferation and villus length, while giving exogenous EGF after the onset of sepsis restores proliferation to levels seen in sham animals and nearly normalizes villus length. Importantly, giving exogenous EGF after CLP results in a 2-fold improvement in survival in septic mice.

Since EGF can have a number of extra-intestinal effects, it was unclear whether the benefits conferred by exogenous EGF were enterocyte-specific. Therefore, similar experiments were performed using transgenic mice with enterocyte-specific overexpression of EGF[31]. Intestine-specific EGF overexpression is sufficient to prevent sepsis-induced decreases in intestinal proliferation and villus length and sepsis-induced increases in gut epithelial apoptosis. Further, intestinal permeability is markedly increased following CLP in wild type mice but permeability is normalized to sham levels in septic transgenic mice that overexpress EGF. This change in barrier function is associated with normalization of claudin-2 expression and localization in transgenic mice that overexpress EGF in their intestinal epithelium. Importantly, enterocyte-specific overexpression of EGF confers a

marked improvement in survival in CLP-induced sepsis, suggesting the protective effects of systemic EGF in septic peritonitis are mediated in a gut-specific fashion.

In addition, to improving survival in CLP, systemic administration of EGF has also been demonstrated to be beneficial in other models of adult critical illness. Specifically, exogenous EGF reduces intestinal injury and improves host survival in animal models of ischemia-reperfusion injury[33,34] and thermal injury[35].

Several lines of evidence have demonstrated an important role for EGF in intestinal repair as well. In a neonatal rat model of necrotizing enterocolitis (NEC), EGF-R is significantly upregulated in the intestinal epithelium, and supplementation of milk formula with EGF decreases the incidence and severity of disease[36]. This protection is associated with decreased intestinal epithelial apoptosis and restoration of intestinal barrier function[28,37]. The EGF/EGF-R signaling axis has also been shown to play a critical role in the adaptive response following short bowel resection since administration of either exogenous EGF or enterocyte-specific overexpression of EGF enhance the adaptive response following short bowel resection[38,39]. On the other hand, this adaptive response is severely impaired in mice that lack functional EGF-R or following pharmacological inhibition of EGF-R[40]. Finally, in patients with peptic ulcer disease, salivary levels of EGF are significantly reduced, and EGF-R expression is 75-fold higher in rats with chemically induced ulcers compared to untreated controls[41]. Patients with peptic ulcer disease treated intravenously with EGF also have improved ulcer healing compared to patients treated with cetraxate hydrochloride[42].

Exogenous EGF appears to be an attractive candidate for clinical trials in critically ill patients. EGF and EGF-R have been targeted for therapeutic use in a large number of diseases, and a federal government registration of clinical trials lists over 200 trials involving or targeting EGF and/or EGF-R[43]. While many of these trials target extraintestinal effects of EGF, beneficial effects in the gut have been noted in clinical trials with EGF. For instance, in patients with ulcerative colitis, treatment with EGF-containing enemas significantly improved scoring of disease activity, sigmoidoscopic findings, and histological grading of injury when compared with placebo[44]. Similarly, a prospective, randomized trial with recombinant EGF in a small group of premature neonates with evidence of NEC demonstrated improved intestinal repair as determined by rectal biopsy specimens[45]. Importantly, no toxicities were reported after EGF administration to these infants. Based upon the benefits of EGF in preclinical trials and its apparent safety when used for short-term therapy in patients, EGF treatment may represent a novel therapeutic in critical illness.

Growth Hormone and Insulin-like Growth Factor-I

Critical illness alters the body's metabolic rate, and a prolonged hypercatabolic state is associated with increased morbidity and mortality[46]. Critical illness is also often associated with alterations in the circulating concentrations or a diminished responsiveness of tissues to anabolic proteins such as IGF-I and growth hormone (GH)[47].

GH is a 22-kDa anabolic protein that can antagonize some of the deleterious effects of hypercatabolism[48]. In critically ill patients, the circulating concentration of GH is markedly elevated. Despite this, there is paradoxical GH resistance, in which GH fails to stimulate IGF-I synthesis in the liver. This has been demonstrated in preclinical trials in sheep that were injected with endotoxin[49], as well as in septic patients who were given exogenous GH but failed to increase circulating IGF-I levels to the same extent as in controls[50].

The receptor for GH is expressed throughout the intestine, which suggests that GH may act to promote epithelial repair during intestinal injury[51]. However, the response to GH in the intestine under both basal and pathophysiologic conditions is incompletely understood.

Potent trophic effects of GH have been demonstrated in the intestine of unmanipulated transgenic mice that overexpress GH[52]. When these transgenic mice are subjected to dextran sodium sulfate (DSS)-induced colitis, they exhibit increased crypt cell proliferation resulting in improved intestinal structure[53]. However, studies examining GH in animal models of short bowel syndrome have shown conflicting results with varying effects on mucosal mass[54,55]. Further, a rat total parenteral nutrition (TPN) model failed to demonstrate a trophic effect of GH on the intestine despite normalized body weight gain and increased plasma IGF-I levels[56,57]. Similarly, rats given GH after severe thermal injury have improved villus morphology compared to controls, but this effect is not mediated by either increased crypt cell proliferation or inhibition of epithelial apoptosis[58].

Critical illness decreases circulating levels of IGF-I[59]. IGF-I is a small polypeptide (70 amino acids) with considerable homology to insulin. The primary biological effect of IGF-I is to stimulate cellular growth and differentiation[60,61]. Multiple studies have demonstrated that IGF-I has beneficial effects on intestinal homeostasis, and specific receptors for IGF-I are present in the gastrointestinal tract of humans and animals. Under normal conditions, transgenic mice that overexpress IGF-I exhibit increased crypt cell mitosis and increased growth of the small intestine[62]. In rats subjected to small bowel resection, administration of IGF-I augments compensatory mucosal hyperplasia and epithelial restitution[63]. Further, IGF-I administration decreases bacterial translocation after severe thermal injury by maintaining intestinal integrity[64,65]. In addition to its effects on intestinal proliferation, IGF-I has also been shown to attenuate intestinal epithelial apoptosis in a murine model of NEC[66] and *in vitro* following H_2O_2-induced injury[67].

Both GH and IGF-1 have been used in clinical trials. Importantly, GH increased morbidity and mortality in critically ill patients in a large prospective, randomized trial[68]. While GH has recently been hypothesized to be of potential benefit in refractory critical illness[69], its utility in this setting is not proven. Long-term GH may be of benefit in patients recovering from critical illness, as opposed to patients who are acutely critically ill. A recent prospective, randomized trial of long-term GH in severely burned children with greater than 40% body surface burn showed improved growth and lean body mass two years after the initial insult[70]. However, GH was initiated after hospital discharge in this study, so they were no longer critically ill by the time GH was initiated.

Therapeutic use of IGF-I has been has not been possible because of adverse side effects such as hypoglycemia, electrolyte imbalances, and cardiac arrest[71,72]. However, when IGF-I is bound to its principle binding protein (IGFBP-3), it has been shown to be safe and efficacious in humans[73–76]. Although IGF-1/IGFBP-3 would be expected to have extraintestinal effects, limited preclinical data suggests it also has beneficial effects on gut integrity. In a rat model of severe thermal injury, intravenous administration of IGF-I in combination with IGFBP-3 stimulated small intestinal epithelial proliferation and increased villus length, crypt depth, and cell number. In addition, IGF-I/IGFBP-3 significantly decreased burn-induced intestinal epithelial apoptosis[77]. These data suggest that IGF-I/IGFBP-3 may be a potential therapeutic agent to improve intestinal integrity in critically ill patients.

Keratinocyte Growth Factor

KGF is a member of the fibroblast growth factor family that stimulates growth and differentiation of epithelial cells in the gastrointestinal tract, lung, and kidney[78]. The receptor for KGF has been found exclusively in the intestinal epithelium, suggesting that KGF acts in a paracrine manner to stimulate epithelial repair in the gut. KGF expression is markedly increased in the mucosa and submucosa of patients with inflammatory bowel

disease, and KGF overexpression correlates with the degree of inflammation[79]. The fact that KGF is upregulated following intestinal injury suggests it plays an important role in normal tissue repair. Administration of KGF to unmanipulated rats causes a marked increase in epithelial proliferation as well as a selective induction of mucin-producing goblet cells throughout the gastrointestinal tract[80]. This induction is associated with increased expression of intestinal trefoil factors, which also play a role in epithelial repair (discussed in more detail below). Intraperitoneal administration of KGF also reduces the extent of intestinal injury in several animal models of colitis[81] while KGF knockout mice subjected to DSS-induced colitis exhibit more severe colonic inflammation and delayed tissue repair than wild-type mice subjected to the same insult[82]. Exogenous KGF also promotes cell survival, as mice subjected given TPN exhibit decreased apoptosis and increased expression of anti-apoptotic Bcl-2 proteins[83].

Chemotherapy and irradiation can compromise epithelial integrity by rapidly killing dividing cells in the mucosa, thereby impairing normal epithelial cell renewal. These treatments are often associated with mucositis, a condition which is characterized by mucosal atrophy, ulceration, barrier dysfunction, and infection[84]. KGF has been successfully used as a pretreatment in animal models of gastrointestinal injury induced by radiation[85,86], chemotherapy[86], or a combination of both[86]. In these models, KGF increases intestinal epithelial cell survival and mucosal thickness which is associated with decreased mortality. Importantly, KGF does not effect the growth rate of epithelial tumors, suggesting it may be a good therapeutic agent to prevent intestinal damage in patients receiving cancer therapy[86]. In contrast, intravenous administration of recombinant KGF failed to induce remission in a Phase II study of patients with active ulcerative colitis[87] although the dose of KGF may have been too low for any beneficial effect to be seen. The effects of KGF in critical illness are unknown.

Hepatocyte Growth Factor

HGF is a mesenchymal-derived pleiotropic protein that regulates cell proliferation, cell survival, motility, morphogenesis, anti-inflammation, and angiogenesis in a wide variety of cells, including gastrointestinal epithelial cells[88,89]. HGF has been shown to accelerate epithelial remodeling after injury by stimulating intestinal epithelial proliferation[90]. Administration of HGF increases mucosal mass and enhances intestinal substrate absorption in rats following small bowel resection[91]. Similarly, HGF stimulates intestinal proliferation leading to preserved villus structure in an animal model of severe thermal injury[92]. The effect of HGF on apoptosis is more variable. HGF administration inhibits intestinal epithelial apoptosis during ischemia-reperfusion injury[93], but has no effect on burn-induced intestinal apoptosis[92].

Several studies have demonstrated that HGF promotes colonic mucosal repair in animal models of colitis. However, the mechanisms underlying protection vary depending on the model and route of HGF treatment. In rats subjected to DSS-induced colitis, continuous intraperitoneal administration of recombinant human HGF reduces colitis-associated weight loss, colonic shortening, and improved colonic erosions, and this is associated with enhanced epithelial regeneration and cellular proliferation [94]. Similarly, daily intravenous administration of recombinant human HGF to rats with TNBS-induced colitis causes a significant reduction in colonic ulcer coverage and colonic shortening, and this is associated with increased epithelial proliferation and decreased inflammatory cell infiltrate in the inflamed colon [95]. The improvements noted with intraperitoneal administration of recombinant human HGF in these models is associated with inhibition of intestinal epithelial apoptosis rather than stimulation of proliferation [96]. Several studies have reported that colitis can also be ameliorated when adenoviral-mediated, liposome-formulated, or naked HGF

gene is administered intrarectally, intramuscularly, or intravenously [97–100]. A potential roadbloack towards using HGF in clinical trials is the observation that it may be a carcinogen since transgenic mouse strains that overexpress HGF exhibit increased rates of benign and malignant liver and mammary gland tumors[101]. The benefits and/or risks of short term usage of HGF in critically ill patients remains to be determined.

Heparin-binding EGF-like Growth Factor

Heparin-binding epidermal growth factor-like growth factor (HB-EGF) was first identified as a 22-kDa glycoprotein in the conditioned medium of cultured human macrophages[102]. A member of the EGF family, HB-EGF is a potent mitogen for a number of cell types, including epithelial cells, fibroblasts, smooth muscle cells, keratinocytes, and renal tubule cells[103]. Expression of endogenous HB-EGF is significantly increased in response to tissue damage, hypoxia, oxidative stress, and during wound healing and regeneration[104]. In cell culture, HB-EGF has been shown to protect intestinal epithelial cells from pro-inflammatory cytokine-induced apoptosis[105]. Pretreatment of intestinal epithelial cells with HB-EGF *in vitro* leads to decreased necrosis, preserved cytoskeletal structure, higher adenosine triphosphate levels, and improved proliferative capacity during recovery from hypoxia[106]. HB-EGF decreases the generation of reactive oxygen species in intestinal epithelial cells after ischemia-reperfusion injury[107]. HB-EGF also preserves the crypt proliferative response and decreases bacterial translocation across intestinal epithelial cell monolayers after ischemia-reperfusion injury, indicating preservation of epithelial integrity[108].

HB-EGF has also been shown to protect the intestine *in vivo*. In a neonatal rat model of NEC, HB-EGF treatment caused increased intestinal proliferation and migration as well as preservation of intestinal epithelial barrier function when compared with untreated animals[109]. Further, in a neonatal hemorrhagic shock model, HB-EGF treatment resulted in increased intestinal blood flow and microcirculatory flow to levels greater than basal pre-shock levels[110]. While these findings are encouraging, the mechanisms for the beneficial effects of HB-EGF remain to be elucidated and its effects in adult models of critical illness have yet to be determined.

Glucagon-like Peptide-2

GLP-2 is a 33 amino acid peptide that is secreted from intestinal endocrine cells in response to nutrient ingestion, which acts as a potent growth factor for the small intestinal epithelium and, to a lesser extent, the large intestinal epithelium [111]. GLP-2 administration significantly improves morbidity and enhances epithelial repair in a diverse number of intestinal injury models, including small bowel resection[112,113], colitis[114,115], and enteritis[116]. The protective effects of GLP-2 are thought to be due to its ability to stimulate crypt cell proliferation, prevent epithelial apoptosis, enhance epithelial barrier function, and reduce intestinal permeability[117–119].

Administration of GLP-2 or a degradation-resistant analogue h[Gly2]GLP-2 has been shown to attenuate intestinal injury in a number of preclinical models of acute disease, including necrotizing pancreatitis[119], burn injury[120], and ischemia-reperfusion injury[121]. In addition, it has been shown to be beneficial in inflammatory bowel disease[114,116,122]. Mice treated with h[Gly2]GLP-2 have preserved mucosal integrity with an increase in intestinal mass as a result of increased proliferation in DSS-induced colitis[122]. Additionally, in a murine model of indomethacin-induced enteritis, h[Gly2]GLP-2 not only stimulated proliferation but also reduced intestinal epithelial apoptosis[116]. Treatment was also associated with decreased mucosal cytokine expression, decreased myeloperoxidase activity, and a marked diminution in bacterial translocation[116]. The trophic and anti-apoptotic activities of GLP-2 have also been demonstrated in rodents and pigs following withdrawal of enteral nutrition where

GLP-2 infusion prevents the development of mucosal atrophy, reduces proteolysis, and decreases crypt cell apoptosis in the small intestine[123,124].

In contrast to the significant amount of evidence supporting GLP-2's usage in preclinical models of gut injury, very limited information is available about its safety and efficacy in humans. In a small pilot study, patients with intestinal failure secondary to short bowel syndrome treated with GLP-2 had improved nutrient absorption, increased body weight, and delayed gastric emptying[125]. Further clinical evaluation of GLP-2 in humans is needed to determine if GLP-2 is effective in reducing intestinal injury or enhancing gut repair in critically ill patients.

Intestinal trefoil factor

The trefoil factor family (TFF) is a group of small protease-resistant peptides that are expressed in mucus-secreting epithelial cells, especially in the gastrointestinal tract. To date, three mammalian TFF members have been identified: TFF1, expressed by surface and pit mucus cells in the stomach; TFF2, expressed by mucus neck and glandular mucus cells of the stomach and Brunner's glands of the proximal duodenum; and TFF3 (also called intestinal trefoil factor, ITF), expressed by goblet cells of the intestine and colon[126].

The trefoil factors have been shown to play an important role in the protection and repair of the gastrointestinal mucosa. Oral administration of TFF2 protects against ethanol-, indomethacin-, and aspirin-induced gastric injury in rats[127,128] and accelerates healing and reduces inflammation in a rat model of inflammatory bowel disease[129]. ITF also promotes epithelial cell migration and inhibits intestinal epithelial apoptosis[130,131]. Mice deficient in ITF are extremely sensitive to mucosal injury and fail to undergo any epithelial repair[132]. Increased ITF expression has been observed in proximity to sites of injury in the gastrointestinal tract, including peptic ulcers and active inflammatory bowel disease. Oral and subcutaneous administration of ITF has also been shown to protect the intestinal epithelium from a variety of insults including ethanol, nonsteroidal anti-inflammatory drugs, and restraint stress. In addition, administration of ITF ameliorates the severity of intestinal injury in a rat model of NEC[133]. Further, ITF has been shown to be effective in both prevention of and healing from acute DSS-induced colitis[134]. ITF also plays a role in protection against and recovery from intestinal mucositis induced by radiation and chemotherapy[135]. Finally, oral administration of either TFF2 or ITF has been shown to significantly reduce mucosal lesions following severe thermal injury[136,137]. These studies show the trefoil factors are important regulators of intestinal epithelial repair in preclinical studies but these have not been translated into clinical findings at the bedside.

Synergism between growth factors

There is some evidence that growth factors may act synergistically to prevent gut injury. When given in isolation, both EGF and growth hormone releasing peptide (GHRP)-6 have beneficial effects in animal models of intestinal injury and repair. However, this effect is additive when EGF and GHRP-6 are given together in an ischemia-reperfusion injury model[138]. In addition, combining glutamine with either GH, IGF-1, or EGF has been demonstrated to have additive or synergistic effects on intestinal growth and adaptation[139–142]. Whether a combination of growth factors listed above will be more effective than a single growth factor in isolation in critical illness has yet to be determined.

Conclusions

In critical illness, the gut functions as the "motor" of the systemic inflammatory response, and maintaining gut barrier function may be a key toward preventing multiple organ

dysfunction syndrome. Growth factors have been shown to play a central role in protecting the gut against injury under both basal conditions and in chronic disease, and increasing evidence suggests they may play a role in acute critical illness as well. Although many of the agents described above have potential therapeutic benefits, EGF is the best studied and may be the most attractive candidate for clinical trials. A synergistic approach combining growth factors may also have significant utility. A more complete understanding of the mechanisms through which growth factors protect the gut is needed, as are strategies for translating preclinical findings to the bedside.

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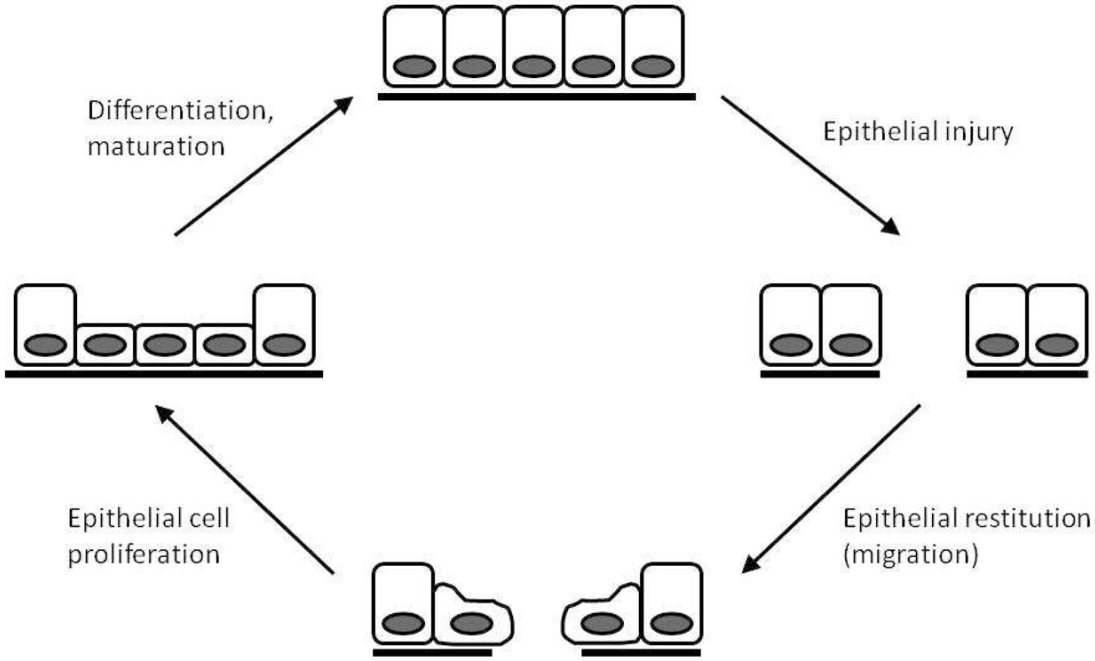

Figure 1.
A simplified model of epithelial injury and restitution. Following epithelial injury, cells depolarize, dedifferentiate, and migrate to cover the denuded area (restitution). Once the epithelial defect is sealed, epithelial cell proliferation is stimulated to replace the cell pool. Epithelial cells then differentiate and mature to become an intact epithelial layer again.

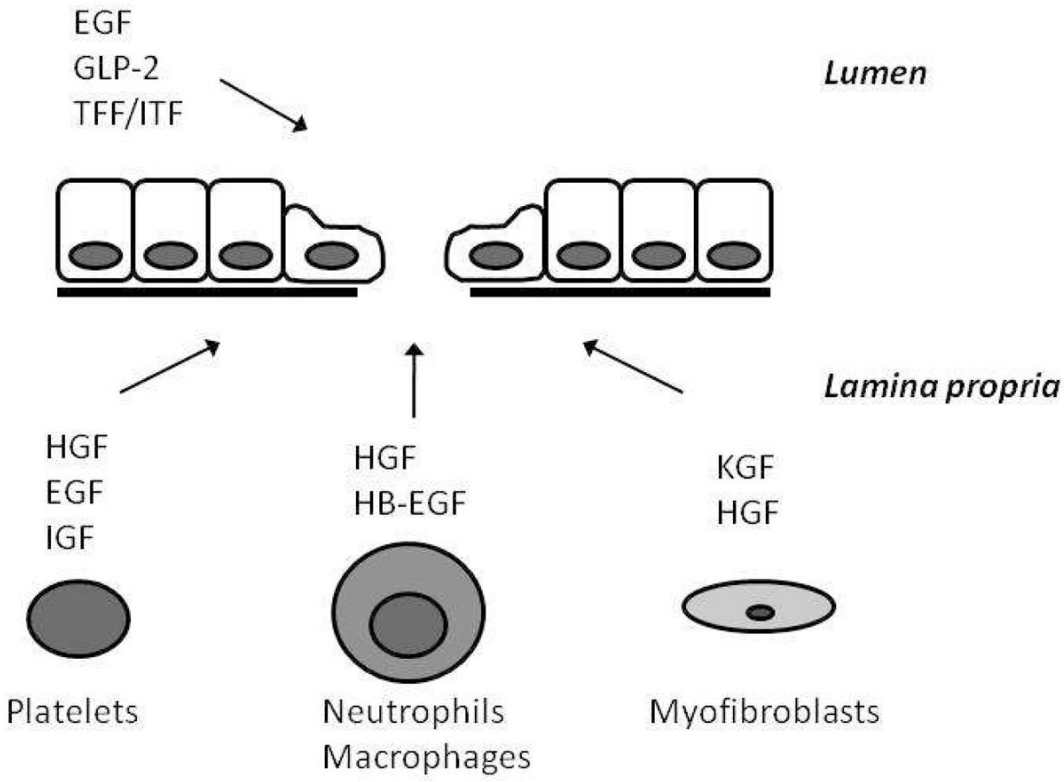

Figure 2.
Several growth factors are involved in preventing or enhancing intestinal epithelial repair. *HGF*, hepatocyte growth factor; *EGF*, epidermal growth factor; *IGF*, insulin-like growth factor; *HB-EGF*, heparin binding EGF-like growth factor; *KGF*, keratinocyte growth factor; *GLP-2*, glucagon-like peptide-2; *TFF*, trefoil factor family; *ITF*, intestinal trefoil factor