World Journal of

Gastroenterology

World Journal of Gastroenterology

Contents

Contents

LETTER TO THE EDITOR

Contents

ABOUT COVER

Associate Editor of *World Journal of Gastroenterology*, Marc D Basson, MD, PhD, MBA, FACS, Senior Associate Dean for Medicine and Research, School of Medicine and Health Sciences, University of North Dakota, 1301 N Columbia Road, Grand Forks, ND 58201, United States. marc.basson@und.edu

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (*WJG*, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJG* mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The *WJG* is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Report® cites the 2020 impact factor (IF) for *WJG* as 5.742; Journal Citation Indicator: 0.79; IF without journal self cites: 5.590; 5-year IF: 5.044; Ranking: 28 among 92 journals in gastroenterology and hepatology; and Quartile category: Q2. The *WJG*'s CiteScore for 2020 is 6.9 and Scopus CiteScore rank 2020: Gastroenterology is 19/136.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Ze-Mao Gong*.

Gut homeostasis, injury, and healing: New therapeutic targets

Sema Oncel, Marc D Basson

Sema Oncel, Marc D Basson, Department of Biomedical Sciences, University of North Dakota School of Medicine and Health Sciences, Grand Forks, ND 58202, United States

Marc D Basson, Department of Surgery, University of North Dakota School of Medicine and Health Sciences, Grand Forks, ND 58202, United States

Marc D Basson, Department of Pathology, University of North Dakota School of Medicine and Health Sciences, Grand Forks, ND 58202, United States

Corresponding author: Marc D Basson, MD, PhD, Professor, Department of Biomedical Sciences, University of North Dakota School of Medicine and Health Sciences, 1301 North Columbia Road, Grand Forks, ND 58202, United States. marc.basson@und.edu

Abstract

The integrity of the gastrointestinal mucosa plays a crucial role in gut homeostasis, which depends upon the balance between mucosal injury by destructive factors and healing *via* protective factors. The persistence of noxious agents such as acid, pepsin, nonsteroidal anti-inflammatory drugs, or *Helicobacter pylori* breaks down the mucosal barrier and injury occurs. Depending upon the size and site of the wound, it is healed by complex and overlapping processes involving membrane resealing, cell spreading, purse-string contraction, restitution, differentiation, angiogenesis, and vasculogenesis, each modulated by extracellular regulators. Unfortunately, the gut does not always heal, leading to such pathology as peptic ulcers or inflammatory bowel disease. Currently available therapeutics such as proton pump inhibitors, histamine-2 receptor antagonists, sucralfate, 5-aminosalicylate, antibiotics, corticosteroids, and immunosuppressants all attempt to minimize or reduce injury to the gastrointestinal tract. More recent studies have focused on improving mucosal defense or directly promoting mucosal repair. Many investigations have sought to enhance mucosal defense by stimulating mucus secretion, mucosal blood flow, or tight junction function. Conversely, new attempts to directly promote mucosal repair target proteins that modulate cytoskeleton dynamics such as tubulin, talin, Ehm², filamin-a, gelsolin, and flightless I or that proteins regulate focal adhesions dynamics such as focal adhesion kinase. This article summarizes the pathobiology of gastrointestinal mucosal healing and reviews potential new therapeutic targets.

Key Words: Intestine; Mucosa; Repair; Restitution; Sheet migration; Stomach ulcer

Core Tip: The integrity of the gastrointestinal mucosa is crucial in gut homeostasis, which depends upon the balance between mucosal injury by destructive factors and healing *via* protective factors. An excess of destructive agents breaks down the mucosal barrier. Upon injury, under physiological conditions, gastrointestinal mucosa heals itself by complex processes. However, the gut may not heal under pathological conditions. Currently available drugs attempt to minimize or reduce injury to the gastrointestinal tract. Recent studies have focused on improving mucosal defense or directly promoting mucosal repair. This article summarizes the pathobiology of gastrointestinal mucosal healing and reviews potential new therapeutic targets.

INTRODUCTION

Upon injury, gastrointestinal (GI) epithelial tissue is capable of renewing itself within hours to months by replacing damaged or dead cells, depending on the site and size of the wound. In order to appreciate potential new therapeutic targets, this review will first summarize the current understanding of the processes of mucosal healing and defense and describe their major extracellular regulators. Then, the importance of the quality of ulcer healing and novel approaches to promote such healing will be reviewed. This review focuses on mucosal injury and repair. Deeper injuries such as a deep ulcer, trauma, fistula, or surgical transection and anastomotic healing all require a complex interaction among endothelial cells, fibroblasts, and other cell types to reconstitute the submucosal and muscular layers of the bowel wall. This is beyond the scope of the current review but has been previously reviewed[1-5]. Angiogenesis is critical to these efforts, and requires a complex interaction between endothelial cells, the extracellular matrix, growth factors and cytokines, and other cell types[6,7].

PHYSIOLOGY OF MUCOSAL HEALING

The integrity of the gastrointestinal mucosa is crucial for gut homeostasis. The gut lining is continuously injured during normal gut function[8] by a variety of noxious luminal substances and abrasive interactions with luminal contents (Figure 1A). However, there is normally an equilibrium between gut injury, mucosal healing, and diverse factors that protect the mucosa[5]. This equilibrium favors healing in a healthy state. Under normal physiological conditions, GI epithelial cells migrate from the base of the crypt to the villi, where their interaction with each other and the extracellular matrix (ECM) is disrupted leading to epithelial cell shedding (anoikis)[9] (Figure 1B).

PROTECTIVE FACTORS FOR THE GASTROINTESTINAL MUCOSA

The gastrointestinal mucosa is protected at three levels: pre-epithelial, epithelial, and sub-epithelial defenses. Pre-epithelial protection, the first line of mucosal defense, is provided by the secretion of mucus, bicarbonate, phospholipids, prostaglandins, and trefoil peptides (Figure 1A and B). These factors not only neutralize the acid but also inactivate pepsin at the gastric mucosal surface. In addition, phospholipids secreted into mucus contribute to the hydrophobicity of mucus and prevent back-diffusion of hydrogen ions[10]. Prostaglandins are abundant in gastric juice. They inhibit acid secretion and stimulate mucus and bicarbonate secretion[11]. Bicarbonate-rich mucus is secreted throughout the GI tract, by mucoid cells in the stomach and goblet cells in the intestines, creating a near-neutral pH at the epithelial surfaces in the GI tract, thereby protecting the GI mucosa against autodigestion by the gastric juice and other noxious agents in the lumen[12,13].

Intestinal epithelial cells consist of four important cell types (Figure 1E and F). Enterocytes and colonocytes are most common in the surface epithelium. They are critical for the digestion and absorption of nutrients. Paneth cells are highly specialized cells located in small intestinal crypts. Paneth cells are essential for the secretion of antimicrobial peptides (AMP) such as defensins. These AMPs modulate the composition of the small intestinal microbiota. Goblet cells produce various types of mucin and are found throughout the GI tract. Similarly, enteroendocrine cells are scattered along with the epithelial cells of the GI tract. They produce and secrete more than 20 different hormones in response to nutrients in the lumen that regulate hunger, appetite, and satiety[14]. Intestinal epithelial

DOI: 10.3748/wjg.v28.i17.1725 **Copyright** ©The Author(s) 2022.
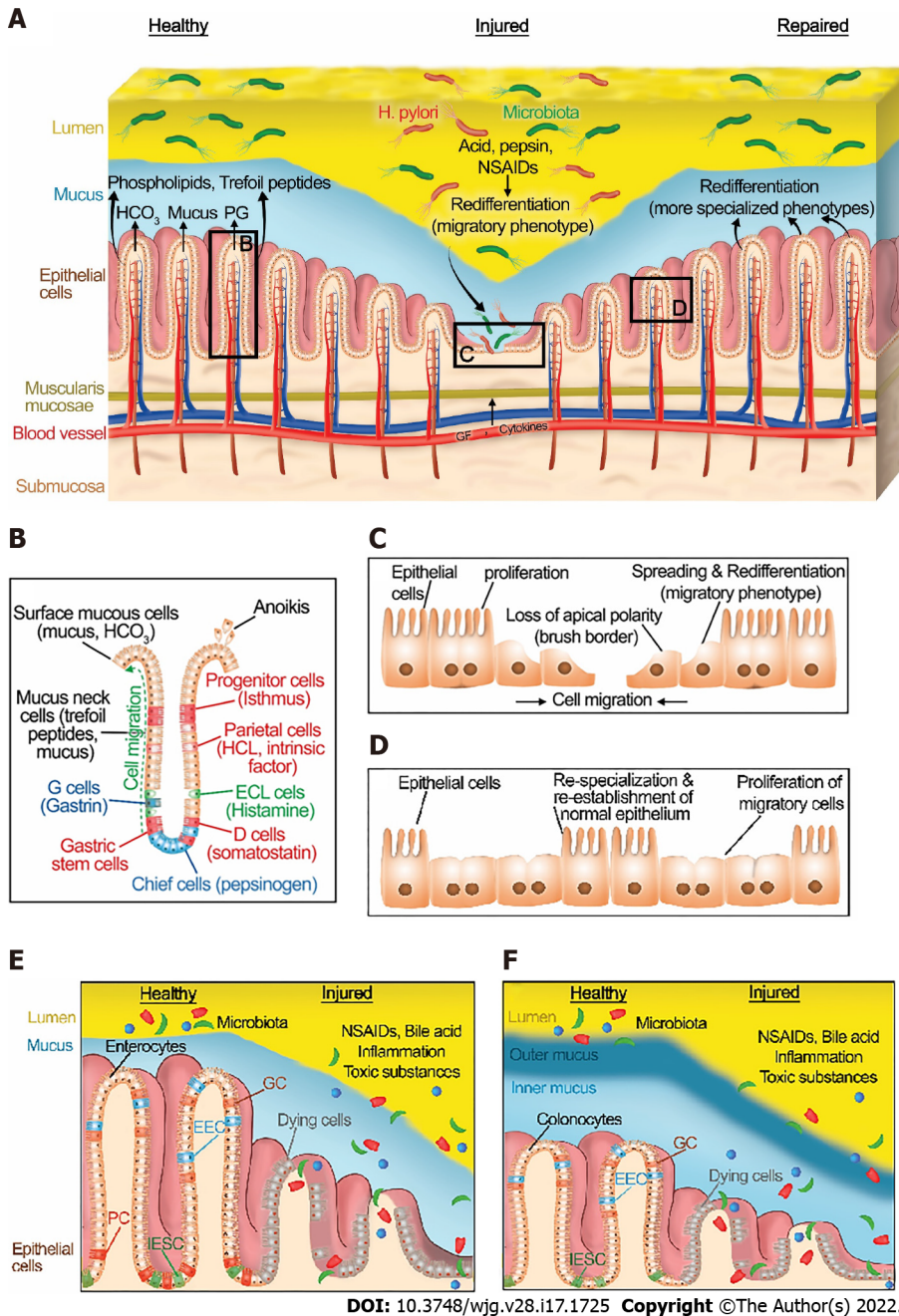
Figure 1 Normal gastrointestinal homeostasis, injury, and healing. A: Structure of gastric epithelium in healthy, injured, and repaired states. A healthy gastric barrier is essential to maintain gastric homeostasis. In a healthy state, there is an equilibrium between gastric injury and mucosal healing. An excess of destructive factors such as acid, pepsin, nonsteroidal anti-inflammatory drugs (NSAIDs), and *H. pylori* leads to gastric barrier disruption. These noxious agents then diffuse deeper into the mucosa and create wounds. Epithelial cells at the edge of the injury redifferentiate to a migratory phenotype and collectively migrate as a sheet to close the wound. After successful restitution, the migrated cells redifferentiate to more specialized phenotypes. B: A diagram depicting the structure and cell types of gastric epithelium. C: In the injured state, epithelial cells at the edge of the wound spread and redifferentiate to a migratory phenotype, losing their classical apical brush border and assuming a more squamous morphology. Then, they migrate as a sheet to cover the injured area, with cells at the front of the migrating sheet transmitting traction forces to cells farther back *via* cell-cell contacts. Epithelial cells behind these migrating cells subsequently proliferate to provide more cells to fully cover larger wounds. D: Cells that have migrated across the defect may themselves then proliferate once the barrier has been reformed. In addition, following migration and proliferation, the migrated cells redifferentiate back to more specialized phenotypes. E: Structure of small intestinal epithelium in healthy and injured states. F: Structure of large intestinal epithelium in healthy and injured states. A healthy intestinal barrier is essential to maintain intestinal homeostasis. In the healthy state, there is an equilibrium between intestinal injury and mucosal healing. An excess of destructive factors such as NSAIDs, inflammation, bile acid, and toxic luminal substances leads to intestinal barrier disruption. These noxious agents then diffuse deeper into the mucosa and create wounds. Epithelial cells at the edge of the injury follow the processes described in the figure legends for in Figure 1C and D. IESC: Intestinal epithelial stem cells; EEC: Enteroendocrine cells; GC: Goblet cells; NSAIDs: Nonsteroidal anti-inflammatory drugs; *H. pylori*: *Helicobacter pylori*; PG: Prostaglandins; ECL cells: Enterochromaffin-like cells; PC: Paneth cells; IESC: Intestinal epithelial stem cells.

stem cells (IESCs) are crucial to maintaining intestinal epithelial function and homeostasis in both the small intestine and large intestine. IESCs divide for self-renewal and generate progenitor cells that undergo differentiation into enterocytes, colonocytes, Paneth cells, goblets cells, and enteroendocrine cells[15].

Epithelial protection represents the second line of defense. GI epithelial cells are connected to each other *via* tight junctions and act as a physical barrier against acid or toxic luminal agents. In addition to stimulating mucus and bicarbonate secretion, prostaglandins reduce the permeability of the epithelium by closing the apical spaces between the epithelial cells, and thus decreasing the exposure of deeper layers along the GI tract to noxious agents by modulating these tight junctions[16]. Tight junction proteins are either transmembrane proteins such as occludin, claudins, and junction adhesion molecule proteins or cytoplasmic plaque proteins such as the zonula occludens proteins. The dysregulation of these proteins *via* toxin exposure or autoimmune diseases such as celiac disease may lead to disruption of gastrointestinal barrier function[17]. For example, ulcerative colitis may alter the intestinal barrier function *via* changing the phosphorylation of colonic claudins[18]. The architecture and function of tight junctions are slightly divergent between the different regions of the GI tract and also between different epithelial cells. For example, disruption of occludin alters intestinal barrier function whereas occludin disruption does not cause barrier dysfunction in the stomach[19]. Moreover, the expression of tight junction proteins varies even among the different epithelial cells. For instance, IESCs and Paneth cells have high occludin levels whereas claudin-1, -2, and -7 expression is elevated in Paneth cells, IESCs, and enterocytes, respectively[20].

The final mucosal defense is sub-epithelial protection through augmentation of mucosal blood flow. Vascular flow not only removes acid rather than allowing it to diffuse deeper into the mucosa but also supplies necessary nutrients and oxygen to the epithelial cells for energy-consuming processes such as ion transport and secretion. Gut epithelial cells undergo continuous dynamic self-renewal in response to the damage caused by destructive factors under normal physiological conditions[21,22].

DRIVERS OF MUCOSAL INJURY

Although the gut epithelium can maintain normal homeostasis in the presence of modest or transient exposure to injurious stimuli, high level or extensive interactions with noxious factors such as excessive secretion of gastric acid and pepsinogen, the substantial inflammation caused by inflammatory bowel disease, or toxic luminal contents including ethanol or medication such as non-steroidal anti-inflammatory drugs (NSAIDs) can unbalance the equilibrium between mucosal injury and healing (Figure 1A).

Gastric juice includes mucus, hydrochloric acid (HCl), bicarbonate, pepsin, and intrinsic factor secreted by mucoid cells, parietal (oxyntic) cells, and chief (zymogenic) cells in the stomach (Figure 1B). *Helicobacter pylori (H. pylori)* infection, a gram-negative bacterium responsible for 90% of duodenal and gastric ulcers, impairs the bicarbonate secretion and promotes gastric acidity as well[23]. Such hyperacidity may injure the mucosa, causing gastritis, duodenitis, peptic ulcer disease (PUD), or gastroesophageal reflux disease (GERD)[24].

The gastrointestinal mucosa is subjected to numerous physical forces such as strain and pressure during both normal gut function and illness. For instance, luminal chyme, peristalsis contractions, rhythmic villous motility, and some pathological conditions such as inflammatory bowel disease (IBD) may adversely impact GI mucosal healing by increasing luminal pressure[25-29]. Such pressure increases have been shown to inhibit mucosal healing, at least in mice, despite increased mucosal proliferation, and appear to act by inhibiting the cell motility required for restitution[28].

The balance between mucosal injury and healing may also be shifted by drugs such as NSAIDs, corticosteroids, bisphosphonates, potassium chloride, steroids, and fluorouracil[23,30,31]. In particular, many studies have documented that NSAIDs decrease mucus hydrophobicity as measured by contact angle goniometry whereas prostaglandins, gastroprotective compounds, increase the contact angle of gastric mucosa[32,33]. NSAIDs, the most commonly prescribed medications, increase the development of ulcers in the upper and lower GI tract by two distinct mechanisms (Figure 2)[34-37].

NSAIDs injure the upper GI mucosa mainly by cyclooxygenase (COX)-1 inhibition, resulting in a decrease in prostaglandins, mucus, and bicarbonate secretion. Moreover, NSAIDs also alter another important component of mucosal defense, the gastric microcirculatory system. Upon irritation, the gastric mucosa normally increases blood flow to remove any toxins, bacterial products, or back-diffusing acid. Impairment of this hyperemic reaction increases the vulnerability of gastric mucosa to damage[38]. Inhibition of prostaglandins, potent vasodilators, by NSAIDs leads to an increase in vascular tone and thus reduces gastric mucosal blood flow[39], consequently, increases ischemic tissue damage and exacerbating the mucosal injury[40]. NSAIDs may also induce local gastric mucosal injury independent of prostaglandin deficiency[41]. NSAIDs may lyse phospholipids from mucosal epithelial cells and may increase mucosal permeability, which then allows mucosal exposure to luminal aggressive factors such as bacteria and gastric acid[42].
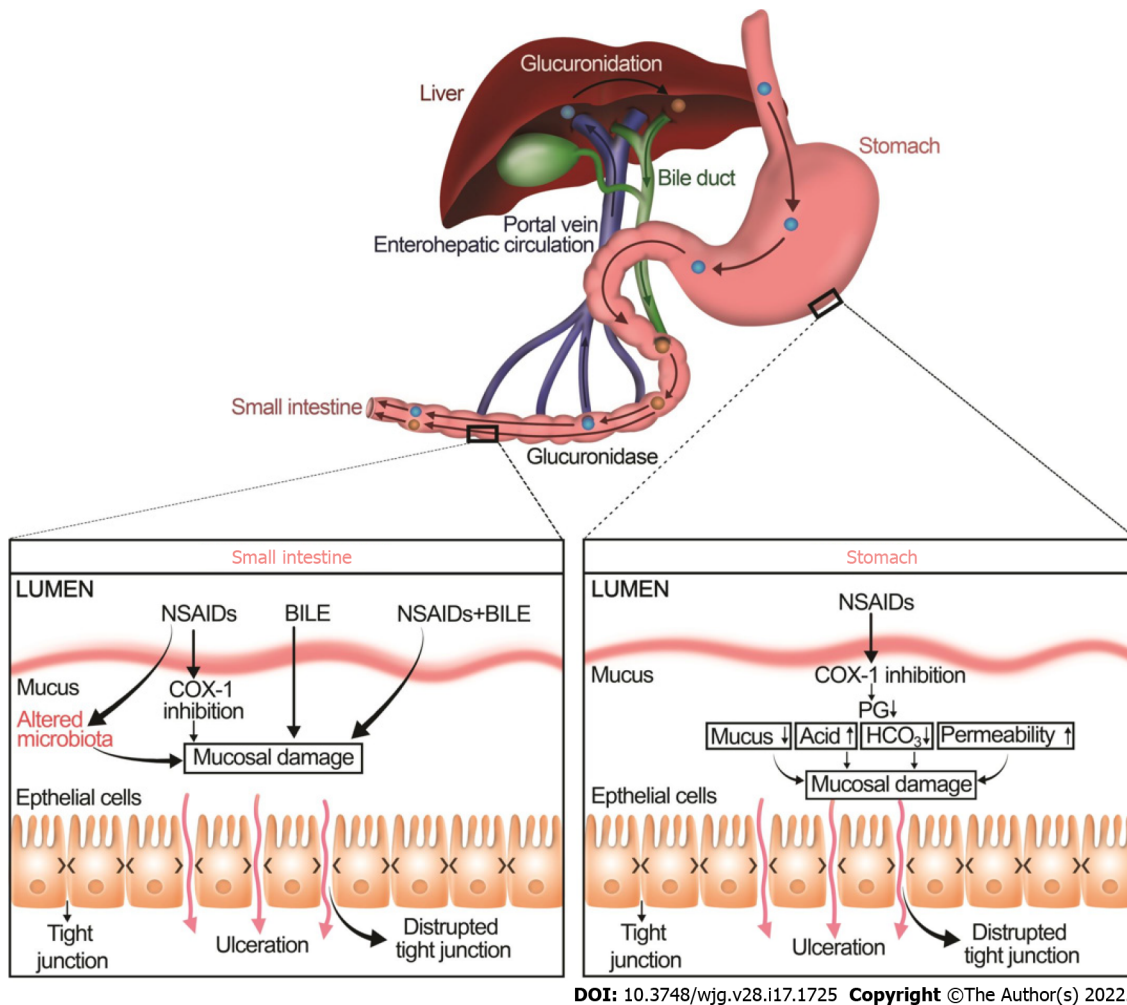
Figure 2 Non-steroidal anti-inflammatory drugs induce mucosal injury in the upper and lower gastrointestinal tract by two distinct mechanisms. In addition to principal luminal aggressors such as acid, pepsin, *Helicobacter pylori* in the stomach and acid, bile, and pathogens in the small intestine, nonsteroidal anti-inflammatory drugs (NSAIDs) increase mucosal damage in both upper and lower GI by two different mechanisms. In the stomach, the inhibition of COX-1 by NSAIDs reduces prostaglandin secretion which in turn reduces mucus and bicarbonate secretion and increases acid secretion, resulting in increased permeability and eventually mucosal damage. In the small intestine, NSAIDs bind to bile in the enterohepatic circulation. This potentiates the mucosal damage caused by bile. NSAIDs also increase mucosal damage in the small intestine by altering the gut microbiota. The NSAID-associated increase in enteric gram-negative bacteria appears to contribute to intestinal lesions by increasing inflammation. NSAIDs: Nonsteroidal anti-inflammatory drugs.

The molecular and cellular mechanisms of NSAID-induced lower GI mucosal injury are clearly distinct from NSAID-induced upper GI injury[42,43]. As in the stomach, NSAIDs may inhibit COX-1 and contribute to mucosal damage. However, unlike gastric injury, the bile acid and intestinal microbiota play a crucial role in the pathophysiology of NSAID-induced intestinal injury[42,44]. NSAIDs and gut microbiota have complex and dynamic interactions. The gut microbiota can alter the efficacy and toxicity of NSAIDs either directly by biotransforming them into metabolites or indirectly by altering the host metabolism (*e.g.*, interfering with hepatic function)[45]. On the other hand, NSAIDs themselves can directly change the composition and function of the gut microbiota or indirectly by altering the physiological functions of the host[45]. For instance, NSAIDs alter the intestinal microbiome by increasing the total number of bacteria and the proportion of gram-negative bacteria, which seems to be linked to the activation of toll-like receptor (TLR) 4 that increases inflammation and contributes to an intestinal injury[46-48].

NSAIDs make complexes with bile acids by glucuronidation in the liver. This interaction alters the stability and structure of bile acids and potentiates bile acid toxicity in the lower GI tract[42]. These NSAID-bile acid complexes are secreted into the duodenum and subsequently reabsorbed back in the ileum *via* the enterohepatic circulation. Within the intestinal lumen, particularly, in the colon, conjugated primary bile acids are deconjugated into more toxic secondary bile acids, mainly by the gram-positive bacteria[49]. There is crosstalk between the microbiome and the bile acids because bile acids can control the composition of the intestinal microbiome, which in turn regulates the composition and size of the bile acid pool[50,51]. Alteration in the colonic microbiota may cause a shift towards to generation of more toxic secondary bile acids, which eventually increase intestinal permeability, particularly in the colon, bacterial translocation, and mucosal inflammation[52-54].

NSAID-induced ulcers are traditionally treated with proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2-antagonists)[55,56], which permit ulcer healing by reducing gastric acid secretion without directly affecting mucosal restitution[5,57,58]. Although PPIs have historically been co-prescribed with NSAIDs to ameliorate gastroduodenal injury and are used to treat NSAID injury, such use may increase the risk of a different problem. There is no evidence that gastric acid plays a key role in the pathogenesis of NSAID-induced lower GI[42,59]. PPIs may worsen NSAID-induced enteropathy by increasing gastric pH and thus changing the enteric microbiome by increasing the number of gram-negative bacteria[35,42,60-62]. Thus, even though PPIs are still recommended to treat upper GI ulcers, their prophylactic use with NSAIDs to prevent upper GI injury is no longer recommended unless the patient has a moderate to high risk of peptic ulcer disease[62,63]. Similar concerns are likely to exist for H-2 blockers.

Inflammatory bowel disease is a broad term to describe disorders including Crohn's disease (CD) and ulcerative colitis (UC) that are characterized by excessive activation of the mucosal immune system to normal microflora. This causes chronic inflammation and damages the gut mucosa[64,65]. Since the etiology of IBD is still unclear, the primary goal of treatment is centered on the elimination of inflammation with medical therapies such as 5-aminosalicylate, antibiotics, corticosteroids, immunosuppressants, and biological therapy[66-68]. Management of IBD with targeted therapies has been discussed in detail in a recent review[68]. However, none of these therapies is perfect, and even if patients achieve symptomatic remission, maintaining that remission can be challenging[69]. Recent evidence highlights the importance of mucosal healing over and above symptomatic remission in the quality of life and long-term prognosis of IBD patients[70-72].

MUCOSAL HEALING PROCESSES

Once an injury has occurred, diverse processes such as redifferentiation to a migratory phenotype[73-75], migration, proliferation, and eventual redifferentiation back to more specialized cells after healing are all regulated by various factors including growth factors, cytokines, physical forces, and the extracellular matrix itself. These coordinate healing of the injury (Figure 1). At the subcellular level, wounding of the apical plasma membrane is common in the epithelial cells of the intact, normal functioning stomach and intestines *in vivo* after mechanical and chemical stressors[8,76,77]. Since maintenance of plasma membrane integrity is essential for cell viability, the wounded cell rapidly repairs the injury to restore internal homeostasis and prevent cell death. Plasma repair processes such as tension reduction, budding, patch, endocytosis, and exocytosis may be triggered by the toxic level of Ca^{2+} influx through the plasma membrane wound to then reseal the injured plasma membrane[78,79].

Relatively small or superficial multicellular mucosal injury undergoes complex wound healing processes that quickly reconstitute the mucosal barrier, depending on the size and depth of the injury. Small wounds, less than eight cells in size, may close by the spreading of neighboring cells and formation of new cell-cell contacts[80,81] or by purse-string wound closure, which involves the formation of a multicellular actin cable purse string around the wound, with actin cables that parallel the wound edge. This then contracts, pulling the adjacent cells together[5,82].

Mucosal injury involving more than eight cells is generally too large for purse-string wound closure. This then requires restitutive epithelial sheet migration to close the injury. Depending on the size and depth of these larger wounds, wound closure will require a longer healing time and may require one or more complex overlapping processes such as differentiation, proliferation, and angiogenesis for wound healing[5,83,84].

Restitution requires a phenotypic redifferentiation. Although some authors describe the initial steps of this process as dedifferentiation, it is the firm opinion of the senior author that this should rather be considered a redifferentiation toward a migratory phenotype. The gut epithelium normally consists of a monostratified layer of differentiated epithelial cells. At the edge of a mucosal wound, epithelial cells change their phenotype from differentiated columnar enterocytes or gastric cells to a migratory phenotype. They lose their typical morphology and (for enterocytes and parietal cells) their microvilli [85], disassemble their apical specialized membrane components[86], flatten out and extend lamellipodia toward the defect. Such migrating cells adopt a squamous morphology with altered integrin[87-89] and cytoskeletal organization[73,85] and specialized cell signaling pathways[90-93] that adapt these cells toward motility (Figure 1C)[73,85,94-96] Moreover, it is worth noting that these signaling events are not only regulated by the activation of signaling proteins but also by the distribution and the amount of the signaling proteins within the migrating cells. For instance, both the actual amount of total focal adhesion kinase (FAK) and the amount of active FAK decrease while the ratio of activated to total FAK increases both in vitro[94] and in vivo[92] as the epithelial cells shift to the migratory phenotype[73]. Similarly, both paxillin protein and tyrosine-phosphorylated paxillin decrease in migrating cells compare to static cells[94]. (Paxillin is an adapter protein critical to focal adhesion complex assembly and disassembly in response to various stimuli.)[97-100]. Total p38, ERK1, and ERK2 proteins do not show differences between migrating and static cells[94]. However, phosphorylated p38 increases, and phosphorylated ERK1 and ERK2 decreases in motile cells compared with nonmigrating

cells[94].

Furthermore, the distribution of these signaling proteins also changes in migratory phenotype. In confluent cells, FAK localizes mainly in a perinuclear pattern while FAK appears explicitly at the cell borders contacting other cells in motile cells, with FAK immunoreactivity decreasing toward the migrating lamellipodia that face the wound edge[94]. In contrast to FAK, paxillin is localized at the lamellipodial edges in migrating cells[94]. The difference is more than semantic because considering these migratory cells as a specialized phenotype opens up the possibility for therapy to modulate that phenotype and thereby promote mucosal healing.

The transverse actin cables that drive purse-string closure for smaller wounds line up parallel to the wound edge at the migrating front, connected by cell-cell contacts, and unite the migrating front, so that these redifferentiated cells collectively migrate as a sheet, a.k.a., restitution, to close the wound (Figure 1C)[101-103]. Slightly deeper wounds that injure the basement membrane expose the cells to the interstitial extracellular matrix. While the basement membrane is predominantly laminin and type IV collagen, the deeper interstitial matrix is rich in type I collagen, across which the cells may migrate more rapidly[104,105].

After the closure of the wound by successful restitution, the migrating cells must redifferentiate back to the more specialized phenotypes required for the normal biology of the mucosa (Figure 1D)[102]. Tarnawski *et al*[106] have demonstrated the critical relationship between defective redifferentiation of these migratory cells and subsequent ulcer recurrence. This will be considered in more detail below.

If the wound surface area is extensive, restitution will likely be insufficient to seal the wound. In this situation, epithelial cell proliferation increases behind the migrating cells to create a larger pool of epithelial cells that can then migrate across and cover the defect (Figure 1C)[107]. However, if the wound extends into deeper layers such as the submucosa and muscularis, these must also be reconstructed for healing by processes beyond the scope of this review. In particular, the reconstitution of nutrient vessels in the submucosa is critical for mucosal wound healing because these provide oxygen and nutrients to the mucosa and remove waste products from the wound site[108,109]. This neovascularization can occur by two distinct processes called angiogenesis and vasculogenesis[110-114]. Angiogenesis refers to the process where new blood vessels are formed from preexisting blood vessels from the wound's adjacent vasculature by sprouting and forming tube-like structures and networks. Vasculogenesis is the *de novo* formation of new blood vessels from the differentiation of bone marrow-derived progenitor stem cells.

RESTITUTION AND QUALITY OF ULCER HEALING AS THE SINE QUA NON FOR WOUND HALING

GI ulcers have traditionally been assessed in clinical settings by a superficial visual endoscopic examination that cannot assess the histological and ultrastructural characteristics of the mucosa or deeper layers. Ulcer recurrence is, unfortunately, common, with rates exceeding 60% if the underlying problem has not been successfully addressed[23]. Recurrence of GI ulcers may be related to many factors including gastric acid secretion, *H. pylori*, NSAIDs, hormonal complications, size and depth of ulcers, anti-ulcer treatment, age, gender, comorbidity, alcohol consumption, and smoking[115-118]. In 1991, Tarnawski *et al*[119] drew attention to the relationship between recurrence of ulcers and ultrastructural abnormalities of deeper layers such as poor `redifferentiation, dilation of glands, reduced mucosal height, and disorganized microvascular network after ulcer healing and proposed the concept of the quality of ulcer healing (QOUH)[119-121]. QOUH is defined as ideal ulcer healing, demonstrating flat ulcer scar, high functional restoration, and histological maturity of the regenerated tissue[115,122]. Many patients treated with PPIs for GI ulcers still suffered from a recurrence of ulcers despite continuous anti-ulcer therapy[115,122-124]. It appears that acid inhibition by PPIs or H_2-antagonists may be insufficient for successful high-quality gastroduodenal ulcer healing because low levels of prostaglandins and high levels of oxygen free radicals entail poor QOUH and thus potentiate ulcer recurrence[122,125,126].

Overall, cumulative data highlight the necessity of QOUH for successful and permanent ulcer healing and point out that contemporary treatments such as PPIs and H_2-antagonists do not always provide such high-quality healing. Therefore, to improve QOUH and decrease the rate of recurrence of GI ulcers, new antiulcer drugs need to be developed to address this. Investigation of the endogenous biologic regulation of mucosal healing, suggests new therapeutic targets, both extracellular and intracellular.

REGULATORS OF MUCOSAL HEALING AND POTENTIAL NEW THERAPEUTIC TARGETS

Supplementing available therapeutic modalities that attempt to minimize or reduce injury, investigators have more recently focused on enhancing mucosal defense or promoting mucosal repair. Both mucosal defense and mucosal healing processes such as restitution, proliferation, angiogenesis, and vasculogenesis can be influenced by acid secretagogues, growth factors, trefoil peptides, cytokines, angiogenic factors, luminal nutrients, and the gastrointestinal microbiota[5,25,127]. In addition, physical forces like strain and pressure, engendered by peristalsis, villous motility, and interaction with luminal contents can influence intestinal epithelial migration and proliferation in a complex manner influenced by the deposition of fibronectin at the site of injury[25,128,129].

Acid secretagogues

Under physiological conditions, the stomach protects itself against various forms of endogenous and exogenous injury, primarily by gastric acid. Gastroprotective mechanisms could be triggered by acid secretagogues such as gastrin, histamine, and thyrotropin-releasing hormone (TRH)[130-132]. Pentagastrin, synthetic gastrin, stimulates gastroprotection in acidified aspirin-induced gastric injury in rats, likely through the activation of histamine-2 receptors, since this is abolished by ranitidine[133]. However, exogenous gastrin protects the rat gastric mucosa against ethanol-induced lesions but not against aspirin-induced gastric damage in rats[134]. Several studies have shown that exogenous histamine-stimulated acid secretion also exerts a protective effect on the gastric mucosa against erosions induced by exogenous HCl in rabbits and frogs by stimulating a greater alkaline tide[135,136]. The central vagal activation by intracisternal injection of the thyrotropin-releasing hormone analog RX77368 enhances mucosal resistance as well by stimulating mucosal blood flow *via* prostaglandin-independent manner which eventually results in the removal of diffused acid from the subepithelial interstitial space [137]. In addition, RX77368 increases the thickness of the mucus gel *via* prostaglandin-dependent manner which slows down the acidification of surface cells[137]. The potential therapeutic adaptation of molecules like RX77368 and other acid secretagogues awaits the further exploration of the disparities between results depending on how the ulcers are induced, as well as challenges with their pharmacologic delivery.

Growth factors, trefoil peptides, and cytokines

Growth factors have diverse pathophysiologic effects, including cytoprotection against destructive agents, epithelial wound healing in response to injury[102,138-140], and angiogenesis[141-144]. Epidermal growth factor (EGF) and transforming growth factor TGF-α are structurally related but different polypeptide growth factors[145]. They both bind to the same cell-surface EGF/TGF-α -receptor and induce generally similar effects[145].

EGF may act in a cytoprotective fashion against mucosal injury by increasing secretion of mucus and bicarbonate[146-148], enhancing blood flow[149-151], or releasing other cytoprotective agents such as prostaglandins[152]. Pretreatment of the stomach[153,154], small intestine[146,155], and colon[149,150] tissues, both *in vivo* and *in vitro*, with EGF decreases mucosal damage by various noxious agents. TGF-α is similarly cytoprotective against gastric injury by ethanol, acetic acid, or aspirin[156,157]. Pretreatment of Caco-2 cells with EGF prevents deoxycholate-induced cellular damage, at least in part, by changes in intracellular calcium content[158], suggesting that EGF exerts direct cytoprotective effects on the epithelium in addition to its effects on blood flow and mucus secretion. Furthermore, because this EGF-induced cytoprotection was observed following only 30 minutes of pretreatment (insufficient for proliferation), these results also suggest that this protection is independent of the mitogenic effects of EGF [158]. Consistent with this idea, adding EGF to the basal surface of rabbit primary gastric epithelial cell monolayers cultured on collagen-coated inserts enhances cytoprotection against apical surface acid by opening the plasma membrane calcium channels and increasing intracellular calcium[159].

In addition to their cytoprotective effects, EGF and TGF-α also promote mucosal healing after injury, stimulating both cell motility and cell proliferation[104,140,154]. Indeed, part of the epithelial mucosal shift to a phenotype adapted to wound healing may be an increase in sensitivity to these growth factors. A recent study demonstrated a 75-fold increase in the number of cells expressing detectable EGF-receptors at the ulcer margin after gastric ulcer induction in rats[160]. Either parenteral or local submucosal intra-ulcer injection of EGF caused a comparable acceleration in the healing of acetic-acid-induced rat gastric ulcers, at least in part by increasing gastric blood flow, decreasing gastric acid secretion, and upregulating COX-2 expression[161]. This is in agreement with previous reports suggesting that COX-2 -influences mucosal healing by regulating both the hyperemic response and epithelial cell proliferation[162,163].

The trefoil peptides may also offer new opportunities for therapy because they are important both for mucosal defense[164-166] (by increasing the viscoelasticity of mucus[167,168]) and mucosal repair[169-171] (by influencing reepithelization[171] and inflammation[172]). The trefoil factor (TFF) family includes TFF1 (also called pS2) expressed in gastric surface mucous cells, TFF2 (also called a spasmolytic polypeptide or SP) produced by mucus-producing gastric mucous neck cells, antral gland cells, and duodenal Brunner's glands, and TFF3 (also called intestinal trefoil factor or ITF), predominantly

produced by goblet cells of the small and large intestine and found abundantly within the mucus. A trefoil domain consists of three loops created by disulfide bonds and all TFFs are comprised of two trefoil domains[173]. Trefoil peptides have been detected in different forms including monomers, dimers, and complexes with other molecules. This influences the strength of their association with mucin[173]. In particular, TFF dimers tightly interact with mucin, increasing the viscosity and elasticity of mucus in comparison to the effect of TFF monomers[167,174].

The TFFs are mostly distributed to the basolateral domain of gastric neck cells and parietal cells in the stomach, the Paneth cells in the small intestine, and the crypt cells in the colon[175]. TFF interactions and specific functions have been discussed in detail in a recent review[176]. A specific TFF receptor has not yet been described. However, some binding and functional studies propose potential TFF receptors that may influence epithelial restitution. TFFs have been reported to bind to transmembrane proteins such as the β1 integrin subunit, CRP-ductin, CXC chemokine receptor (CXCR) 4, CXCR7, proteinase-activated receptor (PAR) 2, PAR4, leucine-rich repeat and Immunoglobin-like domain-containing protein (LINGO) 2, LINGO3, and EGFR[177-181]. TFF3 enhances wound healing by activating EGFR and inducing MAPK[182] and PI3K/Akt signaling pathways *in vitro*[183] whereas TFF2 directly activates CXCR4 and enhances the phosphorylation of ERK1/2 and Akt in gastric epithelial cells[184]. Indeed, the CXCR4 antagonist AMD3100 blocks TFF2-dependent gastric epithelial repair[170]. TFFs, specifically TFF2 and TFF3, regulate epithelial motility *via* integrin-binding and activating focal adhesion kinase as well[175]. TFF2 also promotes cell migration *via* PAR4[185], while TFF3 activates PAR2[186]. Furthermore, TFF2 peptide may be required for optimum activity of EGFR and/or EGF signaling in the stomach because heparin-binding EGF and TGF-α do not induce EGFR activation in the stomachs of *Tff*2 KO mice[177].

Oral administration of trefoil peptides, recombinant human SP, or rat ITF protects the gastric mucosa against ethanol or indomethacin-induced injury in a prostaglandin-independent manner[164]. Similarly, a more recent study has also shown that both parentally and topically applied trefoil peptides reduce ethanol-induced gastric damage, assessed by measurement of gastric mucosal Na⁺ leakage and area of macroscopic injury in rats[187]. Complementing these results, transgenic mice that overexpress human TFF1 display increased resistance to indomethacin-induced small intestinal damage[188] whereas ITF-deficient mice are more prone to ulceration and hemorrhage after oral administration of dextran sulfate sodium (DSS)[189], suggesting that trefoil peptides play an important role in GI mucosal protection. There are likely to be several mechanisms by which the trefoil peptides promote mucosal healing. For instance, exogenous recombinant TFF2 increases epithelial wound healing by decreasing inflammation by negatively regulating IL-12 production from macrophages and dendritic cells[172] whereas exogenous TFF3 activates epithelial wound healing *via* the Na/H exchanger-2[171] and accelerates gastric repair *via* a mechanism that does not require cyclooxygenase activation[170].

TGF-β expression increases in affected mucosa from patients with IBD[190], and at the edge of human gastric and colonic ulcers[92]. Intravenous administration of recombinant bone morphogenetic protein (BMP)-7, a subfamily of TGF-β superfamily, for five days significantly accelerates the healing of trinitrobenzene sulfonic acid (TNBS)-induced colitis in rats by decreasing the expression of pro-inflammatory cytokines (IL-6, TNF-b, ICAM-1)[191]. It should be noted that all of these growth factors and cytokines mentioned in this section interact in a complex fashion, and TGF-β potentiates many of them [127,192,193]. TGF-β also stimulates the synthesis of FAK, a key intracellular signal protein for cell motility and proliferation[92].

Basic fibroblast growth factor (bFGF) and hepatocyte growth factor (HGF) stimulate the healing of acetic acid-induced gastric lesions in rats similarly when administered intraperitoneally or by local submucosal injection at the ulcer site, suggesting that these growth factors also accelerate mucosal repair[161]. The healing of gastric ulcers by bFGF and HGF may involve enhancement of gastric blood blow around the ulcer, suppression of gastric acid secretion, and upregulation of COX-2 expression [161].

When the mucus barrier fails due to overexposure to the noxious agents, acid-back diffusion occurs. In healthy mucosa, increased blood flow response rapidly increases the circulation of pH neutral or slightly alkaline blood through the mucosa to neutralize the diffused acid[103]. Moreover, new vasculature is needed to perfuse and support the newly forming tissue. Therefore, wounds deeper than the epithelial layer also require the formation of new blood vessels in granulation tissue for mucosal healing. Like restitution and proliferation, neovascularization is also modulated by growth factors. Vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), nerve growth factor (NGF), fibroblast growth factor (FGF), and angiopoietin-1(Ang1) are essential for blood vessel regeneration *via* angiogenesis and vasculogenesis following mucosal damage[141-144] and can therefore facilitate deep wound healing[112,193-195]. VEGF, the most potent angiogenic factor, is an indispensable regulator of angiogenesis, making it potentially an ideal candidate to induce angiogenesis/vasculogenesis in mucosal healing. Since VEGF is digested in the lumen by proteolytic enzymes, Jones *et al*[141] used a single injection of a nonviral naked DNA plasmid encoding VEGF and Ang1 directly into the injured area to reduce such deleterious effects. They demonstrated that local gene therapy with a combination of VEGF and Ang1 cDNAs increases gastric ulcer healing and generates more mature vessels and a more complete epithelial structure in acetic acid-induced gastric injury in rats, suggesting that a combination of growth factors may have better therapeutic potency than the use

of any individual factor[141]. Similarly, local gene therapy with serum response factor (SRF) accelerates ulcer healing as well as muscle restoration in acetic acid-induced gastric ulcers in rats[196]. A recent study indicated that angiogenesis and vasculogenesis go hand in hand while forming new vessels in granulation tissue[197]. Delivering such naked genes to a damaged site at endoscopy may be a promising tool to treat such ulcers by increasing the bioavailability of essential GFs.

Cytokines are also involved in the regulation of mucosal barrier function at multiple levels including mucosal homeostasis and inflammation[198]. Proinflammatory cytokines such as tumor necrosis factor (TNF) and IL-13 are upregulated in the inflamed mucosa of IBD patients. Anti-TNF therapy promotes mucosal healing in many patients, but not all patients respond to anti-TNF therapy. Many investigators have therefore focused on other cytokines to improve mucosal barrier function. Unfortunately, many of these attempts have ended disappointingly. For instance, experimental colitis in mice is controlled by using ROR-gamma null Th17 cells, which cannot produce IL17A/F and not induce colitis[199]. However, an anti-IL17A monoclonal antibody not only failed to improve CD in clinical trials but actually aggravated adverse symptoms[200]. IL-13 has seemed similarly promising in pre-clinical studies[201-204], but a trial of IL-13 blockade in UC failed[205]. Such failures of blockade of pro-inflammatory cytokines have recently prompted attempts to use anti-inflammatory IL-10 family cytokines to promote colonic mucosal healing. IL-10 is a major anti-inflammatory cytokine that targets hematopoietic cells in various autoimmune diseases[206]. Gene therapy with a single intravenous injection of an adenoviral vector encoding IL-10 (AdvmuIL-10) diminishes TNBS-induced colitis in mice, decreasing histological injury scores, weight loss, stool markers of inflammation (IL-1β and TNFR-II), and serum amyloid protein in comparison to empty cassette virus (Adv0) or PBS treated mice in TNBS-induced colitis model[207]. Gelatin microspheres containing IL-10 have been developed to increase local bioavailability as a sustained release preparation[208]. Gelatin-microsphere-IL-10 treatment remarkably decreases colonic inflammation in IL-10(-/-) mice compared to treatment with IL-10 alone treatment, at least in part by decreasing IL-12 mRNA expression and down-regulating CD40 expression in macrophage-1 positive cells[208]. However, recombinant IL-10 did not improve clinical symptoms in Crohn's disease[209]. Such disappointing results raise the possibility that manipulating a single cytokine may have unpredictable results because of its effects on the web of compensatory pro-inflammatory and anti-inflammatory cytokine pathways in the inflamed mucosa[198].

One cytokine that may be promising is IL-22. Even though it belongs to the IL-10 family of cytokines, IL-22 is unlike IL-10 in that it targets non-hematopoietic epithelial cells. IL-22 is produced by, apart from the adaptive T cell, innate cells including innate lymphoid cells (ILCs), specifically ILC3 cells in the GI tract. IL-22 has dual roles in inflammation. It can act as a protective (anti-inflammatory) cytokine or a pathological (pro-inflammatory) cytokine[210]. IL-22 influences various tissue epithelial functions such as inflammation[211,212], barrier integrity, regeneration, wound healing[213-215], and host defense against pathogens[216,217]. Beneficial effects of IL-22 have been demonstrated in various murine colitis models[210,218]. However, IL-22 actually appears to worsen the anti-CD40-induced colitis model, in that neutralization of IL-22 reduces the weight loss and colitis scores caused by the anti-CD40 injection and administration of IL-22 then recreates the colitis[219]. Thus, although most animal studies raise the possibility that recombinant human (rh) IL-22 might be a promising therapy for IBD, it remains unclear which effect will be seen in human disease. However, as for other cytokines, the short half-life of rhIL-22 (less than 2 h) limits its clinical applications. Several groups have sought to overcome this obstacle by engineering recombinant fusion proteins with a half-life of 1-2 wk to improve the cytokine's pharmacokinetic properties. Currently, seven IL-22 clinical trials have been investigated for different indications. UTTR1147A is a human IL-22 fusion protein that links the human IL-22 with the Fc portion of human immunoglobulin (Ig) G4, which is prepared for IBD studies[220]. Extensive *in vitro* and *in vivo* studies suggest that UTTR1147A decreases histologic colitis severity by a pathway involving STAT3 activation[220]. These pre-clinical studies demonstrate that UTTR1147A is well tolerated and is not associated with increased inflammatory cytokines in mouse, rat, and monkey studies[220]. A randomized phase-I healthy volunteer study of UTTR1147A demonstrated satisfactory safety and pharmacokinetic profile[221]. A phase-II open-label extension study to evaluate the long-term safety and tolerability of UTTR1147A in patients with moderate to severe UC and CD continues with an estimated completion date in 2025[222].

Therapeutic use of growth factors (except BMP-7) may be limited by their low protein stability[144]. In addition, despite their beneficial effects on the GI tract, long-term or systemic use of any growth factors, trefoil peptides, or cytokines that stimulate cell proliferation, either for cytoprotection or for mucosal healing, may raise concerns about inducing hyperproliferative or dysplastic lesions and potential tumorigenesis. This remains an open issue for such mitogens.

Luminal nutrients and GI microbiota

Luminal nutrients and microbiota are also crucial for the maintenance and repair of the gut mucosa. Short-chain fatty acids (SCFAs) are produced by commensal microbiota, mostly by gram-positive anaerobic bacteria, and are essential for perpetuating intestinal health[223,224]. These SCFAs, especially butyrate, are a major energy source for enterocytes and support gut homeostasis[225-227]. SCFAs may stimulate the differentiation of epithelial cells and their proliferation in vivo[228-230], whereas they promote only differentiation in cell culture models but inhibit proliferation and migration[231-235].

Long known as an energy supply for colonocytes and enterocytes, SCFAs have attracted may also enhance gut barrier function. SCFAs decrease acid-back diffusion by dilating arterial walls and increasing blood flow in gut mucosa[236,237]. In addition, several studies have documented improved intestinal barrier function after SCFA supplementation[238-240]. The SCFAs activate 5' adenosine monophosphate (AMP) kinase and therefore promote tight junction assembly, which in turn enhances intestinal barrier function[241,242]. However, a recent clinical study found no evidence that butyrate monotherapy or a combination of three SCFAs offered any advantage over placebo in improving the disease activity index in ulcerative colitis patients receiving maintenance oral anti-inflammatory medication[243].

Amino acids such as arginine, histidine, and glutamine promote enterocyte proliferation and decrease mucosal permeability by regulating tight junction proteins[244-247]. A recent study proposed that histidine and arginine play an important role in stimulating intestinal restitution, probably stimulating FAK *via* the TGF-β/Smad2 signaling pathway[248]. Glutamine modulates the phenotype of gut epithelial cells by stimulating proliferation and decreasing differentiation *in vitro*[249]. Similarly, many studies have been shown that glutamine also promotes cell proliferation of intestinal epithelial cells in weanling mice[250] and weaning piglets[251], prevents mucosal injury, and regulates enterocyte restitution following acetic acid-induced intestinal injury in rats[252].

Biologically active phospholipids in milk, phosphatidylcholine (PC) and phosphatidic acid (PA), and their metabolites such as lysophosphatidic acid (LPA), all act to increase the barrier function of GI mucosa by increasing the hydrophobicity of the mucus[253]. This makes the tissue non-wettable[10] and provides mucosal protection against aspirin-induced gastric injury in mice[253]. Dietary essential omega-6 fatty acids can enhance the biosynthesis of prostaglandins and increase the GI mucosal barrier [254]. Milk fat globule-epidermal growth factor 8 (MFG-E8), a glycoprotein found in mammary epithelial cells but also produced by lamina propria macrophages, also plays a vital role in modulating enterocyte migration along the crypt-villus axis[255].

Extracellular matrix

Epithelial sheet migration during gut-healing requires crosstalk between focal adhesion (FA) complexes in the lamellipodium and the ECM. The extracellular matrix is an extremely dynamic meshwork comprised of proteins, glycosaminoglycans, and glycoconjugates. Its composition and organization differ between tissue types and with physiological and pathological conditions[256,257]. Besides its structural support, the ECM has a direct role in gastrointestinal wound healing by inducing extensive signaling cascades[258-260]. Plasma and tissue fibronectin accumulating in deeper wounds also help to shift the cells to a phenotype that responds to repetitive deformation by increased motility rather than by classical differentiation[129,261]. ECM remodeling is performed by matrix proteinases such as matrix metalloproteinases (MMPs), lysyl oxidases, and heparanases[262]. The gelatinases, a subgroup of MMPs, consist of two proteinases gelatinase A (MMP-2) and gelatinase B (MMP-9). In particular, MMP-9 is upregulated in the inflamed intestinal mucosa of IBD patients[263-267]. Furthermore, anti-gelatinase neutralizing antibodies have been reported effective in murine DSS-induced colitis[268]. However, a phase II, randomized, placebo-controlled study found that the MMP-9 inhibitor andecaliximab did not induce a significant symptomatic or endoscopic response in patients with active Crohn's disease[269]. This lack of efficacy in Crohn's disease prompted the termination of another clinical trial of the same agent in active ulcerative colitis[270]. Thus, while modulation of matrix metalloproteinases remains an attractive target in IBD, further exploration of the science involved and the reasons for the failure of the clinical trial are needed.

Regulation of cytoskeleton

Epithelial restitution begins at the edge of the wound with the redifferentiation of epithelial cells. Reorganization of the actin cytoskeleton is controlled by the Rho family of GTPases including RhoA, Rac1, and Cdc42 (Figure 1C)[93,271-273]. Epithelial cells then form protrusions called lamellipodia with new focal adhesions (FAs) at the leading edge of the motile cells. The migrating cell increases its contractile forces and disassembles focal adhesions at the rear edge allowing the entire cell to move forward[274-276]. Cell-cell linkages[276] transmit this force to other cells behind the migrating front and stretch the epithelial layer across the wound as a sheet. This sheet migration is characteristic of epithelial cells and differs from the individual cell motility displayed by other cell types.

The cytoskeleton, a complex and dynamic network of actin filaments, microtubules, and intermediate filaments, is also an important factor in wound healing[277]. Epithelial restitution relies on the coordination of forward protrusions and retraction forces at the rear edge, which is orchestrated by the actin and microtubule cytoskeleton[278]. In the lamellipodium, the elongating actin filaments produce the driving forces for the protrusion while microtubules form a polarized network that permits organelle and protein transport throughout the cell during cell migration[279,280]. Intermediate filaments, however, are generally considered for the maintenance of the overall cell shape[280]. Alternatively, or in combination with therapy to reduce ongoing injury by improving mucus barrier function and promoting angiogenesis, one could consider attempting to directly stimulate restitution in order to accelerate barrier reconstitution. Thus, proteins that modulate cytoskeleton dynamics might be targeted for optimal wound repair. Fidgetin-like 2 (FL2), a microtubule-severing enzyme, regulates the
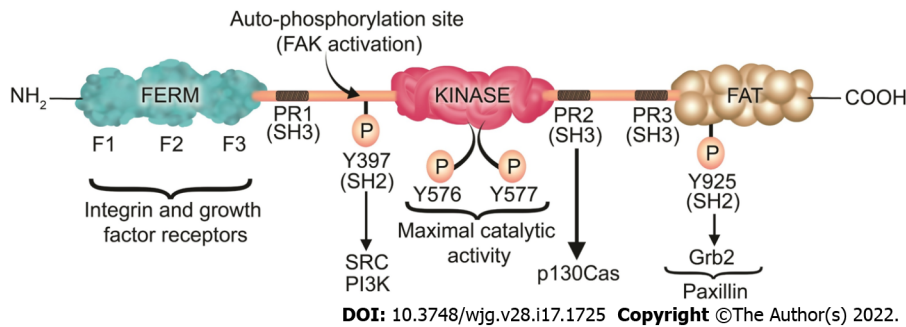
Figure 3 Focal adhesion kinase structure, phosphorylation sites, and its associated proteins. Focal adhesion kinase (FAK) contains an N-terminal band 4.1-ezrin-radixin-moesin (FERM) domain comprised of three lobes (F1, F2, and F3), a central kinase domain, a C-terminal FAT domain, and two linker domains with three PR regions that bind SH3 domain containing protein such as p130Cas. Y397 is the site of the FAK autophosphorylation, crucial for FAK activation, which interacts with proteins containing the SH2 domain such as Src and PI3K. Subsequently to the SH2 binding, Src binds to the PR1 SH3 domain (PXXP) and further phosphorylates the Y576/577 sites on FAK, which are crucial for the maximal catalytic activity of FAK. Further FAK phosphorylation at Y925 creates a binding site for Grb2. The phosphorylation of FAK-Y-925 and subsequent Grb2 binding disassociates paxillin from FAK, which results in FAK release from FAs, thus stimulating FA disassembly. The FERM domain regulates the interactions of FAK with growth factor receptors and integrins. The FAT domain recruits FAK to FAs by associating with paxillin. FERM: Band 4.1-ezrin-radixin-moesin; FAT: Focal adhesion targeting; PR: Proline-rich region; SH: Src homology; P: Phosphorylation.

organization of the microtubule cytoskeleton for faster and successful repair of murine wounds[281]. Actin remodeling proteins such as talin[282], Ehm^2[283], filamin-a[284], gelsolin[285], and flightless I (Flii)[286] have also been identified as potential new targets for improved wound healing. Unlike other members of the gelsolin family, Flii inhibits actin polymerization and FA turnover, thus decreasing migration[286,287]. Flii neutralizing antibodies (FnAb) decreased wound area with a quicker rate of healing in porcine and murine models of wound healing, respectively[288,289].

Regulation of FAs

Cell migration, and consequently wound healing, depend critically on the dynamics of assembly and disassembly of FAs. The subunit composition of integrin receptors and the downstream signaling pathways may vary in different scenarios[290-293]. Nevertheless, integrin binding to ECM triggers focal adhesion formation by recruiting many structural and signaling proteins including FAK, a non-receptor tyrosine kinase[294-298]. FAK regulates FA dynamics both by recruiting other FA proteins such as Src to FA sites and by phosphorylating other signaling and adapter FA proteins such as paxillin and p130Cas [299-301]. FAK also influences the cytoskeletal remodeling essential for cell migration by regulating the Rho family of small GTPases such as Cdc42, Rac1, and RhoA[302-305]. Inhibition of FAK inhibits cell migration[94,298].

Although FAK appears to activate cell motility and promote restitution, and FAK is indeed activated during cell motility, levels of both activated FAK and total FAK protein (including both active and inactive FAK) actually decrease in migrating GI epithelial cells *in vitro* and at the edge of human gastric and colonic ulcers *in vivo* even though the proportion of activated FAK increases (at least *in vitro*)[92, 94]. This reflects decreased FAK synthesis in cells that have adopted the migratory phenotype[306]. This apparently paradoxical reduction in this important protein makes FAK an attractive target for possible therapeutic intervention to promote mucosal healing.

FAK is a 125 kDa protein comprised of an N-terminal FERM (band 4.1-ezrin-radixin-moesin) domain, a central kinase domain, three proline-rich regions that are binding sites for Src homology 3 (SH3) domain-containing proteins, and a C-terminal focal adhesion targeting (FAT) domain (Figure 3).

The FAT domain consists of a four-helix bundle[307] and is critical for targeting FAK to FAs *via* binding to paxillin[308]. In an inactive (autoinhibited) state there is an interaction between the FERM and kinase domains which prevents FAK autophosphorylation at Y397[309]. Upon competitive binding of candidate activating proteins such as the cytoplasmic regions of β-integrins or growth factor receptors on the F2 domain of FERM, the autoinhibited conformation of FAK is disassembled[310]. This conformational change allows Y397 phosphorylation, a key event in FAK activation[311]. In a subsequent step, Src is recruited and activated *via* SH2 binding to pY397 and SH3 binding to the PxxP sequence in the linker region, an essential step in promoting cell migration[311]. Then, Src phosphorylates the activation loop residues Y576 and Y577 of FAK and it acquires full catalytic activity after phosphorylation of the activation loop[312]. Phosphorylation of FAK at tyrosine 925 residue creates an SH2 binding site for the growth factor receptor-bound protein 2 (Grb2), adaptor protein[313]. The Grb2 binding site at FAK-Y-925 overlaps with one of the paxillin binding sites in the FAT domain of FAK[313]. The binding of Grb2 disassociates paxillin from FAK and potentiates the release of FAK from FAs[313]. On the other hand, paxillin acts as a scaffold protein for ERK signaling[305]. Subsequently, ERK may modulate FA turnover by further phosphorylating paxillin[305]. Therefore, Paxillin and Grb2 are critical FA proteins that interact with FAK and play an important role in FA turnover[97,313].
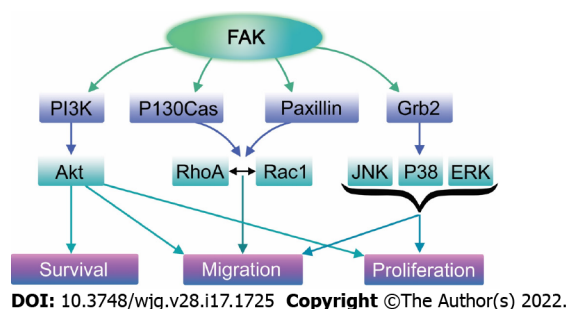
Figure 4 Focal adhesion kinase plays a crucial role in several signaling pathways that promote migration, proliferation, and survival. Upon its activation, focal adhesion kinase (FAK) directly binds PI3K, leading to the activation of Akt. Activated Akt then stimulates numerous cellular functions including cell survival, proliferation, and migration *via* various signaling cascades depending on the cell type and species. In addition, FAK may recruit Grb2 and subsequently activate the Ras/Raf/MAPK pathway, enhancing cell proliferation and motility. Finally, FAK may directly bind to paxillin and p130Cas, promoting lamellipodium formation, and thus migration *via* Rac GTPase activation.
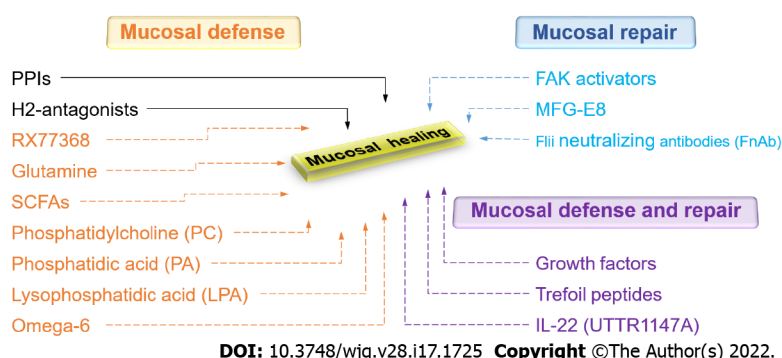
Figure 5 Current and promising new therapeutic approaches to gastrointestinal mucosal healing. Green represents currently available drugs. Red represents promising new therapeutic approaches that increase mucosal defense. Blue represents promising new therapeutic approaches that promote mucosal repair. Purple represents promising new therapeutic approaches that stimulate both mucosal defense and repair. PPIs: Proton pump inhibitors; H2-antagonists: Histamine-2 receptor antagonists; RX77368: The thyrotropin-releasing hormone analog; SCFAs: Short-chain fatty acids; FAK: Focal adhesion kinase; MFG-E8: Milk fat globule-epidermal growth factor 8; Flii: Flightless I.

FAK has both a structural role as a scaffold for protein-protein interactions and a kinase function that phosphorylates many substrates in diverse signaling events[314,315]. Its non-kinase scaffolding function allows several different proteins to bind its N-terminal FERM domain and C-terminal FAT domain, tethering them into complexes (Figure 3). For instance, FAK may regulate cell migration serving as a scaffold for Src phosphorylation of p130Cas[316] in FAs. Similarly, nuclear FAK may promote cell survival functioning as a scaffold to stabilize p53-Mdm² complexes, promoting p53 ubiquitination and proteasomal degradation[317]. On the other hand, in its kinase signaling capacity, FAK triggers many downstream signals including the Ras/Raf/MAPK[97,296,318-320], p130Cas-Crk[321-324], and phosphatidylinositol 3-kinase (PI3K)-Akt pathways[317], which in turn coordinate to regulate cell proliferation, migration, and survival (Figure 4)[313,325].

Recent evidence suggests that direct modulation of FAK activity is possible, practical, and effective *via* small molecule FAK activators[326]. A novel small molecule with drug-like properties, ZINC40099027 (ZN27), that mimics the FERM domain of FAK has been identified from the ZINC database and activates FAK in human intestinal epithelial cells without activating Pyk2, the closest paralogue of FAK, or Src, another canonical nonreceptor tyrosine kinase within focal adhesions[327]. Indeed, ZN27 directly activates both full-length 125 kDa and its 35 kDa kinase domain, increasing the maximal activity (V_{max}) of FAK, suggesting that ZN27 is a highly potent and selective activator acting allosterically on the 35 kDa FAK kinase domain[328]. ZN27 not only activates FAK but also stimulates intestinal epithelial migration *in vitro* and mucosal healing in mice after ischemic injury or injury by indomethacin[327]. ZN27 also activates FAK in gastric epithelial cells and promotes gastric mucosal healing in mice subjected to chronic ongoing injury by aspirin[58]. Structure-activity-relationship studies have developed a library of novel FAK activators based on ZN27, that have drug-like properties, activate FAK, and stimulate epithelial sheet migration in vitro[329]. At least one such molecule (dubbed compound 3) demonstrates reasonable drug-like properties based on *in vitro, in vivo*, and *in silico* results with no obvious toxicity[329]. Further development of this lead molecule may offer the potential for a new therapeutic approach to actually stimulate mucosal healing by activating FAK.

CONCLUSION

Given the enormous impact of GI mucosal healing on human health, there is certainly a need to expand therapeutic options in this regard. A new understanding of the biology of mucosal healing suggests several different possibilities (Figure 5). These include FAK activators, UTTR1147A, endoscopic gene therapy for angiogenic growth factors, mucus barrier enhancement *via* the thyrotropin-releasing hormone analog RX77368 or trefoil peptides, enhanced energy for the mucosa with butyrate, and attempts to increase the regenerative ability of the epithelium with growth factors, cytokines, or trefoil peptides. Future work will determine which of these potentially promising avenues will prove successful and will need to balance their effects against potential risks and issues, including bioavailability, mitogenicity, and tumorigenesis.

FOOTNOTES

Author contributions: Oncel S and Basson MD equally contributed to this manuscript with regards to the conception and structure of the manuscript in addition to the literature review; The final draft of the manuscript was read and approved by all the authors.

ORCID number: Sema Oncel 0000-0001-5551-2271; Marc D Basson 0000-0001-9696-2789.

REFERENCES

1   **Li C**, Kuemmerle JF. Mechanisms that mediate the development of fibrosis in patients with Crohn's disease. *Inflamm Bowel Dis* 2014; **20**: 1250-1258 [PMID: 24831560 DOI: 10.1097/MIB.0000000000000043]

2   **Aviello G**, Knaus UG. ROS in gastrointestinal inflammation: Rescue Or Sabotage? *Br J Pharmacol* 2017; **174**: 1704-1718 [PMID: 26758851 DOI: 10.1111/bph.13428]

3   **Lam A**, Fleischer B, Alverdy J. The Biology of Anastomotic Healing-the Unknown Overwhelms the Known. *J Gastrointest Surg* 2020; **24**: 2160-2166 [PMID: 32524361 DOI: 10.1007/s11605-020-04680-w]

4   **Mortensen JH**, Lindholm M, Langholm LL, Kjeldsen J, Bay-Jensen AC, Karsdal MA, Manon-Jensen T. The intestinal tissue homeostasis - the role of extracellular matrix remodeling in inflammatory bowel disease. *Expert Rev Gastroenterol Hepatol* 2019; **13**: 977-993 [PMID: 31587588 DOI: 10.1080/17474124.2019.1673729]

5   **Basson MD**. Hierarchies of healing in gut mucosal injury. *J Physiol Pharmacol* 2017; **68**: 789-795 [PMID: 29550790]

6   **Powell RJ**, Bhargava J, Basson MD, Sumpio BE. Coculture conditions alter endothelial modulation of TGF-beta 1 activation and smooth muscle growth morphology. *Am J Physiol* 1998; **274**: H642-H649 [PMID: 9486269 DOI: 10.1152/ajpheart.1998.274.2.H642]

7   **Ahluwalia A**, Patel K, Hoa N, Brzozowska I, Jones MK, Tarnawski AS. Melatonin ameliorates aging-related impaired angiogenesis in gastric endothelial cells *via* local actions on mitochondria and VEGF-survivin signaling. *Am J Physiol Gastrointest Liver Physiol* 2021; **321**: G682-G689 [PMID: 34668398 DOI: 10.1152/ajpgi.00101.2021]

8   **McNeil PL**, Ito S. Gastrointestinal cell plasma membrane wounding and resealing in vivo. *Gastroenterology* 1989; **96**: 1238-1248 [PMID: 2703112 DOI: 10.1016/S0016-5085(89)80010-1]

9   **Liu X**, Xiao L, Wang JY. Posttranscriptional control of intestinal epithelium homeostasis by RNA-binding protein HuR. *Sheng Li Xue Bao* 2020; **72**: 325-335 [PMID: 32572430 DOI: 10.13294/j.aps.2020.0034]

10 **Lichtenberger LM**. The hydrophobic barrier properties of gastrointestinal mucus. *Annu Rev Physiol* 1995; **57**: 565-583 [PMID: 7778878 DOI: 10.1146/ANNUREV.PH.57.030195.003025]

11 **Wallace JL**. Prostaglandins, NSAIDs, and gastric mucosal protection: why doesn't the stomach digest itself? *Physiol Rev* 2008; **88**: 1547-1565 [PMID: 18923189 DOI: 10.1152/physrev.00004.2008]

12 **Matúz J**. Role of mucus in mucosal protection through ethanol and pepsin damage models. *Acta Physiol Hung* 1992; **80**: 189-194 [PMID: 1345186]

13   **Atuma C**, Strugala V, Allen A, Holm L. The adherent gastrointestinal mucus gel layer: thickness and physical state in vivo. *Am J Physiol Gastrointest Liver Physiol* 2001; **280**: G922-G929 [PMID: 11292601 DOI: 10.1152/AJPGI.2001.280.5.G922]

14   **Gribble FM**, Reimann F. Function and mechanisms of enteroendocrine cells and gut hormones in metabolism. *Nat Rev Endocrinol* 2019; **15**: 226-237 [PMID: 30760847 DOI: 10.1038/s41574-019-0168-8]

15   **Moorefield EC**, Andres SF, Blue RE, Van Landeghem L, Mah AT, Santoro MA, Ding S. Aging effects on intestinal homeostasis associated with expansion and dysfunction of intestinal epithelial stem cells. *Aging (Albany NY)* 2017; **9**: 1898-1915 [PMID: 28854151 DOI: 10.18632/aging.101279]

16   **Takezono Y**, Joh T, Oshima T, Suzuki H, Seno K, Yokoyama Y, Alexander JS, Itoh M. Role of prostaglandins in maintaining gastric mucus-cell permeability against acid exposure. *J Lab Clin Med* 2004; **143**: 52-58 [PMID: 14749685 DOI: 10.1016/J.LAB.2003.09.004]

17   **Slifer ZM**, Blikslager AT. The Integral Role of Tight Junction Proteins in the Repair of Injured Intestinal Epithelium. *Int J Mol Sci* 2020; **21** [PMID: 32024112 DOI: 10.3390/IJMS21030972]

18   **Li J**, Li YX, Chen MH, Li J, Du J, Shen B, Xia XM. Changes in the phosphorylation of claudins during the course of experimental colitis. *Int J Clin Exp Pathol* 2015; **8**: 12225-12233 [PMID: 26722407]

19   **Saitou M**, Furuse M, Sasaki H, Schulzke JD, Fromm M, Takano H, Noda T, Tsukita S. Complex phenotype of mice lacking occludin, a component of tight junction strands. *Mol Biol Cell* 2000; **11**: 4131-4142 [PMID: 11102513 DOI: 10.1091/MBC.11.12.4131]

20   **Pearce SC**, Al-Jawadi A, Kishida K, Yu S, Hu M, Fritzky LF, Edelblum KL, Gao N, Ferraris RP. Marked differences in tight junction composition and macromolecular permeability among different intestinal cell types. *BMC Biol* 2018; **16**: 19 [PMID: 29391007 DOI: 10.1186/s12915-018-0481-z]

21   **Liu Y**, Chen YG. Intestinal epithelial plasticity and regeneration *via* cell dedifferentiation. *Cell Regen* 2020; **9**: 14 [PMID: 32869114 DOI: 10.1186/s13619-020-00053-5]

22   **Xiao S**, Zhou L. Gastric Stem Cells: Physiological and Pathological Perspectives. *Front Cell Dev Biol* 2020; **8**: 571536 [PMID: 33043003 DOI: 10.3389/fcell.2020.571536]

23   **Malik TF**, Gnanapandithan K, Singh K.   Peptic Ulcer Disease. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021: 170-179

24   **Osefo N**, Ito T, Jensen RT. Gastric acid hypersecretory states: recent insights and advances. *Curr Gastroenterol Rep* 2009; **11**: 433-441 [PMID: 19903418 DOI: 10.1007/S11894-009-0067-6]

25   **Basson MD**. Paradigms for mechanical signal transduction in the intestinal epithelium. Category: molecular, cell, and developmental biology. *Digestion* 2003; **68**: 217-225 [PMID: 14739529 DOI: 10.1159/000076385]

26   **Gayer CP**, Basson MD. The effects of mechanical forces on intestinal physiology and pathology. *Cell Signal* 2009; **21**: 1237-1244 [PMID: 19249356 DOI: 10.1016/j.cellsig.2009.02.011]

27   **Kellow JE**, Phillips SF. Altered small bowel motility in irritable bowel syndrome is correlated with symptoms. *Gastroenterology* 1987; **92**: 1885-1893 [PMID: 3569764 DOI: 10.1016/0016-5085(87)90620-2]

28   **Flanigan TL**, Owen CR, Gayer C, Basson MD. Supraphysiologic extracellular pressure inhibits intestinal epithelial wound healing independently of luminal nutrient flow. *Am J Surg* 2008; **196**: 683-689 [PMID: 18954600 DOI: 10.1016/j.amjsurg.2008.07.016]

29   **Andersson P**, Olaison G, Hallböök O, Boeryd B, Sjödahl R. Increased anal resting pressure and rectal sensitivity in Crohn's disease. *Dis Colon Rectum* 2003; **46**: 1685-1689 [PMID: 14668596 DOI: 10.1007/BF02660776]

30   **Yamamoto K**, Kishino M, Nakamura S, Tokushige K. Symptoms and Upper Gastrointestinal Mucosal Injury Associated with Bisphosphonate Therapy. *Intern Med* 2019; **58**: 1049-1056 [PMID: 30626809 DOI: 10.2169/internalmedicine.1271-18]

31   **Scarpignato C**, Bjarnason I. Drug-Induced Small Bowel Injury: a Challenging and Often Forgotten Clinical Condition. *Curr Gastroenterol Rep* 2019; **21**: 55 [PMID: 31720893 DOI: 10.1007/s11894-019-0726-1]

32   **Lugea A**, Antolín M, Mourelle M, Guarner F, Malagelada JR. Deranged hydrophobic barrier of the rat gastroduodenal mucosa after parenteral nonsteroidal anti-inflammatory drugs. *Gastroenterology* 1997; **112**: 1931-1939 [PMID: 9178685 DOI: 10.1053/GAST.1997.V112.PM9178685]

33   **Kaunitz JD**. Barrier function of gastric mucus. *Keio J Med* 1999; **48**: 63-68 [PMID: 10405521 DOI: 10.2302/KJM.48.63]

34   **Davis JS**, Lee HY, Kim J, Advani SM, Peng HL, Banfield E, Hawk ET, Chang S, Frazier-Wood AC. Use of non-steroidal anti-inflammatory drugs in US adults: changes over time and by demographic. *Open Heart* 2017; **4**: e000550 [PMID: 28674622 DOI: 10.1136/openhrt-2016-000550]

35   **Gwee KA**, Goh V, Lima G, Setia S. Coprescribing proton-pump inhibitors with nonsteroidal anti-inflammatory drugs: risks versus benefits. *J Pain Res* 2018; **11**: 361-374 [PMID: 29491719 DOI: 10.2147/JPR.S156938]

36   **Higuchi K**, Umegaki E, Watanabe T, Yoda Y, Morita E, Murano M, Tokioka S, Arakawa T. Present status and strategy of NSAIDs-induced small bowel injury. *J Gastroenterol* 2009; **44**: 879-888 [PMID: 19568687 DOI: 10.1007/s00535-009-0102-2]

37   **Yamagata M**, Hiraishi H. [Prevalence and incidence of NSAID-induced gastrointestinal ulcers and bleeding]. *Nihon Rinsho* 2007; **65**: 1749-1753 [PMID: 17926519]

38   **Holzer P**, Livingston EH, Guth PH. Sensory neurons signal for an increase in rat gastric mucosal blood flow in the face of pending acid injury. *Gastroenterology* 1991; **101**: 416-423 [PMID: 2065919 DOI: 10.1016/0016-5085(91)90020-L]

39   **Wallace JL**. Pathogenesis of NSAID-induced gastroduodenal mucosal injury. *Best Pract Res Clin Gastroenterol* 2001; **15**: 691-703 [PMID: 11566035 DOI: 10.1053/BEGA.2001.0229]

40   **Maricic N**, Ehrlich K, Gretzer B, Schuligoi R, Respondek M, Peskar BM. Selective cyclo-oxygenase-2 inhibitors aggravate ischaemia-reperfusion injury in the rat stomach. *Br J Pharmacol* 1999; **128**: 1659-1666 [PMID: 10588920 DOI: 10.1038/SJ.BJP.0702966]

41   **Matsui H**, Shimokawa O, Kaneko T, Nagano Y, Rai K, Hyodo I. The pathophysiology of non-steroidal anti-inflammatory drug (NSAID)-induced mucosal injuries in stomach and small intestine. *J Clin Biochem Nutr* 2011; **48**: 107-111 [PMID: 21373261 DOI: 10.3164/jcbn.10-79]

42   **Wallace JL**. NSAID gastropathy and enteropathy: distinct pathogenesis likely necessitates distinct prevention strategies. *Br J Pharmacol* 2012; **165**: 67-74 [PMID: 21627632 DOI: 10.1111/j.1476-5381.2011.01509.x]

43   **Whittle BJ**. Mechanisms underlying intestinal injury induced by anti-inflammatory COX inhibitors. *Eur J Pharmacol* 2004; **500**: 427-439 [PMID: 15464050 DOI: 10.1016/J.EJPHAR.2004.07.042]

44   **Otani K**, Tanigawa T, Watanabe T, Shimada S, Nadatani Y, Nagami Y, Tanaka F, Kamata N, Yamagami H, Shiba M, Tominaga K, Fujiwara Y, Arakawa T. Microbiota Plays a Key Role in Non-Steroidal Anti-Inflammatory Drug-Induced Small Intestinal Damage. *Digestion* 2017; **95**: 22-28 [PMID: 28052268 DOI: 10.1159/000452356]

45   **Maseda D**, Ricciotti E. NSAID-Gut Microbiota Interactions. *Front Pharmacol* 2020; **11**: 1153 [PMID: 32848762 DOI: 10.3389/fphar.2020.01153]

46   **Tai FWD**, McAlindon ME. NSAIDs and the small bowel. *Curr Opin Gastroenterol* 2018; **34**: 175-182 [PMID: 29438118 DOI: 10.1097/MOG.0000000000000427]

47   **Zhou Y**, Dial EJ, Doyen R, Lichtenberger LM. Effect of indomethacin on bile acid-phospholipid interactions: implication for small intestinal injury induced by nonsteroidal anti-inflammatory drugs. *Am J Physiol Gastrointest Liver Physiol* 2010; **298**: G722-G731 [PMID: 20203063 DOI: 10.1152/ajpgi.00387.2009]

48   **Watanabe T**, Higuchi K, Kobata A, Nishio H, Tanigawa T, Shiba M, Tominaga K, Fujiwara Y, Oshitani N, Asahara T, Nomoto K, Takeuchi K, Arakawa T. Non-steroidal anti-inflammatory drug-induced small intestinal damage is Toll-like receptor 4 dependent. *Gut* 2008; **57**: 181-187 [PMID: 17639086 DOI: 10.1136/gut.2007.125963]

49   **Hegyi P**, Maléth J, Walters JR, Hofmann AF, Keely SJ. Guts and Gall: Bile Acids in Regulation of Intestinal Epithelial Function in Health and Disease. *Physiol Rev* 2018; **98**: 1983-2023 [PMID: 30067158 DOI: 10.1152/physrev.00054.2017]

50   **Ticho AL**, Malhotra P, Dudeja PK, Gill RK, Alrefai WA. Intestinal Absorption of Bile Acids in Health and Disease. *Compr Physiol* 2019; **10**: 21-56 [PMID: 31853951 DOI: 10.1002/cphy.c190007]

51   **Urdaneta V**, Casadesús J. Interactions between Bacteria and Bile Salts in the Gastrointestinal and Hepatobiliary Tracts. *Front Med (Lausanne)* 2017; **4**: 163 [PMID: 29043249 DOI: 10.3389/fmed.2017.00163]

52   **Murakami Y**, Tanabe S, Suzuki T. High-fat Diet-induced Intestinal Hyperpermeability is Associated with Increased Bile Acids in the Large Intestine of Mice. *J Food Sci* 2016; **81**: H216-H222 [PMID: 26595891 DOI: 10.1111/1750-3841.13166]

53   **Higashimura Y**, Naito Y, Takagi T, Uchiyama K, Mizushima K, Ushiroda C, Ohnogi H, Kudo Y, Yasui M, Inui S, Hisada T, Honda A, Matsuzaki Y, Yoshikawa T. Protective effect of agaro-oligosaccharides on gut dysbiosis and colon tumorigenesis in high-fat diet-fed mice. *Am J Physiol Gastrointest Liver Physiol* 2016; **310**: G367-G375 [PMID: 26767984 DOI: 10.1152/ajpgi.00324.2015]

54   **Ajouz H**, Mukherji D, Shamseddine A. Secondary bile acids: an underrecognized cause of colon cancer. *World J Surg Oncol* 2014; **12**: 164 [PMID: 24884764 DOI: 10.1186/1477-7819-12-164]

55   **Tuskey A**, Peura D. The use of H2 antagonists in treating and preventing NSAID-induced mucosal damage. *Arthritis Res Ther* 2013; **15** Suppl 3: S6 [PMID: 24267478 DOI: 10.1186/ar4178]

56   **Sturkenboom MC**, Burke TA, Tangelder MJ, Dieleman JP, Walton S, Goldstein JL. Adherence to proton pump inhibitors or H2-receptor antagonists during the use of non-steroidal anti-inflammatory drugs. *Aliment Pharmacol Ther* 2003; **18**: 1137-1147 [PMID: 14653834 DOI: 10.1046/J.1365-2036.2003.01795.X]

57   **Vanderhoff BT**, Tahboub RM. Proton pump inhibitors: an update. *Am Fam Physician* 2002; **66**: 273-280 [PMID: 12152963]

58   **Oncel S**, Gupta R, Wang Q, Basson MD. ZINC40099027 Promotes Gastric Mucosal Repair in Ongoing Aspirin-Associated Gastric Injury by Activating Focal Adhesion Kinase. *Cells* 2021; **10** [PMID: 33920786 DOI: 10.3390/cells10040908]

59   **Hunt RH**, Lanas A, Stichtenoth DO, Scarpignato C. Myths and facts in the use of anti-inflammatory drugs. *Ann Med* 2009; **41**: 423-437 [PMID: 19430988 DOI: 10.1080/07853890902887295]

60   **Mahmoud YI**, Abd El-Ghffar EA. Spirulina ameliorates aspirin-induced gastric ulcer in albino mice by alleviating oxidative stress and inflammation. *Biomed Pharmacother* 2019; **109**: 314-321 [PMID: 30396089 DOI: 10.1016/j.biopha.2018.10.118]

61   **Handa O**, Naito Y, Fukui A, Omatsu T, Yoshikawa T. The impact of non-steroidal anti-inflammatory drugs on the small intestinal epithelium. *J Clin Biochem Nutr* 2014; **54**: 2-6 [PMID: 24426183 DOI: 10.3164/jcbn.13-84]

62   **Marlicz W**, Loniewski I, Grimes DS, Quigley EM. Nonsteroidal anti-inflammatory drugs, proton pump inhibitors, and gastrointestinal injury: contrasting interactions in the stomach and small intestine. *Mayo Clin Proc* 2014; **89**: 1699-1709 [PMID: 25440891 DOI: 10.1016/j.mayocp.2014.07.015]

63   **Szeto CC**, Sugano K, Wang JG, Fujimoto K, Whittle S, Modi GK, Chen CH, Park JB, Tam LS, Vareesangthip K, Tsoi KKF, Chan FKL. Non-steroidal anti-inflammatory drug (NSAID) therapy in patients with hypertension, cardiovascular, renal or gastrointestinal comorbidities: joint APAGE/APLAR/APSDE/APSH/APSN/PoA recommendations. *Gut* 2020; **69**: 617-629 [PMID: 31937550 DOI: 10.1136/gutjnl-2019-319300]

64   **Kaser A**, Zeissig S, Blumberg RS. Inflammatory bowel disease. *Annu Rev Immunol* 2010; **28**: 573-621 [PMID: 20192811 DOI: 10.1146/annurev-immunol-030409-101225]

65   **Danese S**, Fiocchi C. Ulcerative colitis. *N Engl J Med* 2011; **365**: 1713-1725 [PMID: 22047562 DOI: 10.1056/NEJMra1102942]

66   **Klenske E**, Bojarski C, Waldner M, Rath T, Neurath MF, Atreya R. Targeting mucosal healing in Crohn's disease: what the clinician needs to know. *Therap Adv Gastroenterol* 2019; **12**: 1756284819856865 [PMID: 31236140 DOI: 10.1177/1756284819856865]

67   **Strober W**, Fuss I, Mannon P. The fundamental basis of inflammatory bowel disease. *J Clin Invest* 2007; **117**: 514-521 [PMID: 17332878 DOI: 10.1172/JCI30587]

68   **Baumgart DC**, Le Berre C. Newer Biologic and Small-Molecule Therapies for Inflammatory Bowel Disease. *N Engl J Med* 2021; **385**: 1302-1315 [PMID: 34587387 DOI: 10.1056/nejmra1907607]

69   **Matsuoka K**, Kobayashi T, Ueno F, Matsui T, Hirai F, Inoue N, Kato J, Kobayashi K, Koganei K, Kunisaki R, Motoya S, Nagahori M, Nakase H, Omata F, Saruta M, Watanabe T, Tanaka T, Kanai T, Noguchi Y, Takahashi KI, Watanabe K,

Hibi T, Suzuki Y, Watanabe M, Sugano K, Shimosegawa T. Evidence-based clinical practice guidelines for inflammatory bowel disease. *J Gastroenterol* 2018; **53**: 305-353 [PMID: 29429045 DOI: 10.1007/s00535-018-1439-1]

70   **Atreya R**, Neurath MF. Current and Future Targets for Mucosal Healing in Inflammatory Bowel Disease. *Visc Med* 2017; **33**: 82-88 [PMID: 28612022 DOI: 10.1159/000458006]

71   **Pineton de Chambrun G**, Peyrin-Biroulet L, Lémann M, Colombel JF. Clinical implications of mucosal healing for the management of IBD. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 15-29 [PMID: 19949430 DOI: 10.1038/nrgastro.2009.203]

72   **Lichtenstein GR**, Rutgeerts P. Importance of mucosal healing in ulcerative colitis. *Inflamm Bowel Dis* 2010; **16**: 338-346 [PMID: 19637362 DOI: 10.1002/ibd.20997]

73   **Basson MD**, Rashid Z, Turowski GA, West AB, Emenaker NJ, Sgambati SA, Hong F, Perdikis DM, Datta S, Madri JA. Restitution at the cellular level: regulation of the migrating phenotype. *Yale J Biol Med* 1996; **69**: 119-129 [PMID: 9112743]

74   **Modlin IM**, Basson MD, Soroka CJ, Wright N, Poulsom R, Chinnery R, Hanby A, Patel K, Rogers L, Alison M. Ulcer-induced alterations in cell phenotype and growth factor expression. *Eur J Gastroenterol* 1993; **93**: S59-S67

75   **Basson MD**, Modlin IM, Turowski G, Madri JA. Enterocyte-matrix interactions in the healing of mucosal injury. *Eur J Gastroenterol* 1993; **5**: S21-S28

76   **McNeil PL**, Terasaki M. Coping with the inevitable: how cells repair a torn surface membrane. *Nat Cell Biol* 2001; **3**: E124-E129 [PMID: 11331898 DOI: 10.1038/35074652]

77   **Cooper ST**, McNeil PL. Membrane Repair: Mechanisms and Pathophysiology. *Physiol Rev* 2015; **95**: 1205-1240 [PMID: 26336031 DOI: 10.1152/physrev.00037.2014]

78   **Andrews NW**, Corrotte M. Plasma membrane repair. *Curr Biol* 2018; **28**: R392-R397 [PMID: 29689221 DOI: 10.1016/j.cub.2017.12.034]

79   **Blazek AD**, Paleo BJ, Weisleder N. Plasma Membrane Repair: A Central Process for Maintaining Cellular Homeostasis. *Physiology (Bethesda)* 2015; **30**: 438-448 [PMID: 26525343 DOI: 10.1152/physiol.00019.2015]

80   **Walsh MF**, Thamilselvan V, Grotelueschen R, Farhana L, Basson M. Absence of adhesion triggers differential FAK and SAPKp38 signals in SW620 human colon cancer cells that may inhibit adhesiveness and lead to cell death. *Cell Physiol Biochem* 2003; **13**: 135-146 [PMID: 12876384 DOI: 10.1159/000071864]

81   **Williams JM**, Duckworth CA, Burkitt MD, Watson AJ, Campbell BJ, Pritchard DM. Epithelial cell shedding and barrier function: a matter of life and death at the small intestinal villus tip. *Vet Pathol* 2015; **52**: 445-455 [PMID: 25428410 DOI: 10.1177/0300985814559404]

82   **Bement WM**, Forscher P, Mooseker MS. A novel cytoskeletal structure involved in purse string wound closure and cell polarity maintenance. *J Cell Biol* 1993; **121**: 565-578 [PMID: 8486737 DOI: 10.1083/jcb.121.3.565]

83   **Landén NX**, Li D, Ståhle M. Transition from inflammation to proliferation: a critical step during wound healing. *Cell Mol Life Sci* 2016; **73**: 3861-3885 [PMID: 27180275 DOI: 10.1007/s00018-016-2268-0]

84   **Zundler S**, Tauschek V, Neurath MF. Immune Cell Circuits in Mucosal Wound Healing: Clinical Implications. *Visc Med* 2020; **36**: 129-136 [PMID: 32355670 DOI: 10.1159/000506846]

85   **Ubelmann F**, Chamaillard M, El-Marjou F, Simon A, Netter J, Vignjevic D, Nichols BL, Quezada-Calvillo R, Grandjean T, Louvard D, Revenu C, Robine S. Enterocyte loss of polarity and gut wound healing rely upon the F-actin-severing function of villin. *Proc Natl Acad Sci U S A* 2013; **110**: E1380-E1389 [PMID: 23520048 DOI: 10.1073/pnas.1218446110]

86   **Albers TM**, Lomakina I, Moore RP. Fate of polarized membrane components and evidence for microvillus disassembly on migrating enterocytes during repair of native intestinal epithelium. *Lab Invest* 1995; **73**: 139-148 [PMID: 7603035]

87   **Goggins BJ**, Chaney C, Radford-Smith GL, Horvat JC, Keely S. Hypoxia and Integrin-Mediated Epithelial Restitution during Mucosal Inflammation. *Front Immunol* 2013; **4**: 272 [PMID: 24062740 DOI: 10.3389/fimmu.2013.00272]

88   **Keely S**, Glover LE, MacManus CF, Campbell EL, Scully MM, Furuta GT, Colgan SP. Selective induction of integrin beta1 by hypoxia-inducible factor: implications for wound healing. *FASEB J* 2009; **23**: 1338-1346 [PMID: 19103643 DOI: 10.1096/fj.08-125344]

89   **Lotz MM**, Rabinovitz I, Mercurio AM. Intestinal restitution: progression of actin cytoskeleton rearrangements and integrin function in a model of epithelial wound healing. *Am J Pathol* 2000; **156**: 985-996 [PMID: 10702414 DOI: 10.1016/S0002-9440(10)64966-8]

90   **Tétreault MP**, Chailler P, Beaulieu JF, Rivard N, Ménard D. Specific signaling cascades involved in cell spreading during healing of micro-wounded gastric epithelial monolayers. *J Cell Biochem* 2008; **105**: 1240-1249 [PMID: 18802922 DOI: 10.1002/jcb.21924]

91   **Sanders MA**, Basson MD. Collagen IV regulates Caco-2 migration and ERK activation *via* alpha1beta1- and alpha2beta1-integrin-dependent Src kinase activation. *Am J Physiol Gastrointest Liver Physiol* 2004; **286**: G547-G557 [PMID: 14604860 DOI: 10.1152/ajpgi.00262.2003]

92   **Walsh MF**, Ampasala DR, Hatfield J, Vander Heide R, Suer S, Rishi AK, Basson MD. Transforming growth factor-beta stimulates intestinal epithelial focal adhesion kinase synthesis *via* Smad- and p38-dependent mechanisms. *Am J Pathol* 2008; **173**: 385-399 [PMID: 18583311 DOI: 10.2353/ajpath.2008.070729]

93   **Sanders MA**, Ampasala D, Basson MD. DOCK5 and DOCK1 regulate Caco-2 intestinal epithelial cell spreading and migration on collagen IV. *J Biol Chem* 2009; **284**: 27-35 [PMID: 19004829 DOI: 10.1074/jbc.M808010200]

94   **Yu CF**, Sanders MA, Basson MD. Human caco-2 motility redistributes FAK and paxillin and activates p38 MAPK in a matrix-dependent manner. *Am J Physiol Gastrointest Liver Physiol* 2000; **278**: G952-G966 [PMID: 10859226 DOI: 10.1152/ajpgi.2000.278.6.g952]

95   **Olson AD**. Contraction of collagen gels by intestinal epithelial cells depends on microfilament function. *Dig Dis Sci* 1993; **38**: 388-395 [PMID: 8444067 DOI: 10.1007/BF01316489]

96   **Yu CF**, Basson MD. Matrix-specific FAK and MAPK reorganization during Caco-2 cell motility. *Microsc Res Tech* 2000; **51**: 191-203 [PMID: 11054869 DOI: 10.1002/1097-0029(20001015)51:2<191::AID-JEMT10>3.0.CO;2-1]

97   **López-Colomé AM**, Lee-Rivera I, Benavides-Hidalgo R, López E. Paxillin: a crossroad in pathological cell migration. *J Hematol Oncol* 2017; **10**: 50 [PMID: 28214467 DOI: 10.1186/s13045-017-0418-y]

98   **Conway WC**, Van der Voort van Zyp J, Thamilselvan V, Walsh MF, Crowe DL, Basson MD. Paxillin modulates squamous cancer cell adhesion and is important in pressure-augmented adhesion. *J Cell Biochem* 2006; **98**: 1507-1516 [PMID: 16552730 DOI: 10.1002/JCB.20819]

99   **Ibata N**, Terentjev EM. Development of Nascent Focal Adhesions in Spreading Cells. *Biophys J* 2020; **119**: 2063-2073 [PMID: 33068539 DOI: 10.1016/j.bpj.2020.09.037]

100   **Legerstee K**, Houtsmuller AB. A Layered View on Focal Adhesions. *Biology (Basel)* 2021; **10** [PMID: 34827182 DOI: 10.3390/BIOLOGY10111189]

101   **Blikslager AT**, Moeser AJ, Gookin JL, Jones SL, Odle J. Restoration of barrier function in injured intestinal mucosa. *Physiol Rev* 2007; **87**: 545-564 [PMID: 17429041 DOI: 10.1152/physrev.00012.2006]

102   **Sturm A**, Dignass AU. Epithelial restitution and wound healing in inflammatory bowel disease. *World J Gastroenterol* 2008; **14**: 348-353 [PMID: 18200658 DOI: 10.3748/wjg.14.348]

103   **Laine L**, Takeuchi K, Tarnawski A. Gastric mucosal defense and cytoprotection: bench to bedside. *Gastroenterology* 2008; **135**: 41-60 [PMID: 18549814 DOI: 10.1053/j.gastro.2008.05.030]

104   **Basson MD**, Modlin IM, Madri JA. Human enterocyte (Caco-2) migration is modulated in vitro by extracellular matrix composition and epidermal growth factor. *J Clin Invest* 1992; **90**: 15-23 [PMID: 1634605 DOI: 10.1172/JCI115828]

105   **Basson MD**, Modlin IM, Flynn SD, Jena BP, Madri JA. Independent modulation of enterocyte migration and proliferation by growth factors, matrix proteins, and pharmacologic agents in an in vitro model of mucosal healing. *Surgery* 1992; **112**: 299-307; discussion 307 [PMID: 1353641]

106   **Tarnawski A**, Tanoue K, Santos AM, Sarfeh IJ. Cellular and molecular mechanisms of gastric ulcer healing. Is the quality of mucosal scar affected by treatment? *Scand J Gastroenterol Suppl* 1995; **210**: 9-14 [PMID: 8578218 DOI: 10.3109/00365529509090261]

107   **Gao JH**, Guo LJ, Huang ZY, Rao JN, Tang CW. Roles of cellular polyamines in mucosal healing in the gastrointestinal tract. *J Physiol Pharmacol* 2013; **64**: 681-693 [PMID: 24388882]

108   **Basson MD**. Gut mucosal healing: is the science relevant? *Am J Pathol* 2002; **161**: 1101-1105 [PMID: 12368182 DOI: 10.1016/S0002-9440(10)64385-4]

109   **Baatar D**, Jones MK, Tsugawa K, Pai R, Moon WS, Koh GY, Kim I, Kitano S, Tarnawski AS. Esophageal ulceration triggers expression of hypoxia-inducible factor-1 alpha and activates vascular endothelial growth factor gene: implications for angiogenesis and ulcer healing. *Am J Pathol* 2002; **161**: 1449-1457 [PMID: 12368217 DOI: 10.1016/S0002-9440(10)64420-3]

110   **Dudar GK**, D'Andrea LD, Di Stasi R, Pedone C, Wallace JL. A vascular endothelial growth factor mimetic accelerates gastric ulcer healing in an iNOS-dependent manner. *Am J Physiol Gastrointest Liver Physiol* 2008; **295**: G374-G381 [PMID: 18583458 DOI: 10.1152/ajpgi.90325.2008]

111   **Bauer SM**, Bauer RJ, Velazquez OC. Angiogenesis, vasculogenesis, and induction of healing in chronic wounds. *Vasc Endovascular Surg* 2005; **39**: 293-306 [PMID: 16079938 DOI: 10.1177/153857440503900401]

112   **Tarnawski AS**, Ahluwalia A, Jones MK. Angiogenesis in gastric mucosa: an important component of gastric erosion and ulcer healing and its impairment in aging. *J Gastroenterol Hepatol* 2014; **29** Suppl 4: 112-123 [PMID: 25521743 DOI: 10.1111/jgh.12734]

113   **Sen S**, McDonald SP, Coates PT, Bonder CS. Endothelial progenitor cells: novel biomarker and promising cell therapy for cardiovascular disease. *Clin Sci (Lond)* 2011; **120**: 263-283 [PMID: 21143202 DOI: 10.1042/CS20100429]

114   **Sato T**, Amano H, Ito Y, Eshima K, Minamino T, Ae T, Katada C, Ohno T, Hosono K, Suzuki T, Shibuya M, Koizumi W, Majima M. Vascular endothelial growth factor receptor 1 signaling facilitates gastric ulcer healing and angiogenesis through the upregulation of epidermal growth factor expression on VEGFR1+CXCR4 + cells recruited from bone marrow. *J Gastroenterol* 2014; **49**: 455-469 [PMID: 23982810 DOI: 10.1007/s00535-013-0869-z]

115   **Arakawa T**, Kobayashi K. Quality of ulcer healing--a new concept to rank healed peptic ulcers. *Gastroenterol Jpn* 1993; **28** Suppl 5: 158-162 [PMID: 8103020 DOI: 10.1007/BF02989227]

116   **Seo JH**, Hong SJ, Kim JH, Kim BW, Jee SR, Chung WC, Shim KN, Baik GH, Kim SS, Kim SG, Kim JI. Long-Term Recurrence Rates of Peptic Ulcers without Helicobacter pylori. *Gut Liver* 2016; **10**: 719-725 [PMID: 27114412 DOI: 10.5009/gnl15262]

117   **Pantea M**, Negovan A, Banescu C, Bataga S, Neagoe R, Mocan S, Iancu M. Factors Associated with Recurrent Ulcers in Patients with Gastric Surgery after More Than 15 Years: A Cross-Sectional Single-Center Study. *Gastroenterol Res Pract* 2018; **2018**: 8319481 [PMID: 30524477 DOI: 10.1155/2018/8319481]

118   **Ramakrishnan K**, Salinas RC. Peptic ulcer disease. *Am Fam Physician* 2007; **76**: 1005-1012 [PMID: 17956071]

119   **Tarnawski A**, Douglass TG, Stachura J, Krause WJ. Quality of gastric ulcer healing: histological and ultrastructural assessment. *Aliment Pharmacol Ther* 1991; **5** Suppl 1: 79-90 [PMID: 1888836 DOI: 10.1111/J.1365-2036.1991.TB00751.X]

120   **Tarnawski A**, Stachura J, Krause WJ, Douglass TG, Gergely H. Quality of gastric ulcer healing: a new, emerging concept. *J Clin Gastroenterol* 1991; **13** Suppl 1: S42-S47 [PMID: 1719066 DOI: 10.1097/00004836-199112001-00007]

121   **Arakawa T**, Watanabe T, Tanigawa T, Tominaga K, Fujiwara Y, Morimoto K. Quality of ulcer healing in gastrointestinal tract: its pathophysiology and clinical relevance. *World J Gastroenterol* 2012; **18**: 4811-4822 [PMID: 23002355 DOI: 10.3748/WJG.V18.I35.4811]

122   **Young Oh T**, Ok Ahn B, Jung Jang E, Sang Park J, Jong Park S, Wook Baik H, Hahm KB. Accelerated Ulcer Healing and Resistance to Ulcer Recurrence with Gastroprotectants in Rat Model of Acetic Acid-induced Gastric Ulcer. *J Clin Biochem Nutr* 2008; **42**: 204-214 [PMID: 18545642 DOI: 10.3164/jcbn.2008030]

123   **Kangwan N**, Park JM, Kim EH, Hahm KB. Quality of healing of gastric ulcers: Natural products beyond acid suppression. *World J Gastrointest Pathophysiol* 2014; **5**: 40-47 [PMID: 24891974 DOI: 10.4291/wjgp.v5.i1.40]

124   **Nebiki H**, Arakawa T, Higuchi K, Kobayashi K. Quality of ulcer healing influences the relapse of gastric ulcers in humans. *J Gastroenterol Hepatol* 1997; **12**: 109-114 [PMID: 9083911 DOI: 10.1111/J.1440-1746.1997.TB00393.X]

125   **Niv Y**. H pylori recurrence after successful eradication. *World J Gastroenterol* 2008; **14**: 1477-1478 [PMID: 18330934 DOI: 10.3748/WJG.14.1477]

126   **Tarnawski A**, Hollander D, Krause WJ, Dabros W, Stachura J, Gergely H. "Healed" experimental gastric ulcers remain histologically and ultrastructurally abnormal. *J Clin Gastroenterol* 1990; **12** Suppl 1: S139-S147 [PMID: 2212540 DOI: 10.1097/00004836-199001001-00024]

127   **Iizuka M**, Konno S. Wound healing of intestinal epithelial cells. *World J Gastroenterol* 2011; **17**: 2161-2171 [PMID: 21633524 DOI: 10.3748/wjg.v17.i17.2161]

128   **Kovalenko PL**, Flanigan TL, Chaturvedi L, Basson MD. Influence of defunctionalization and mechanical forces on intestinal epithelial wound healing. *Am J Physiol Gastrointest Liver Physiol* 2012; **303**: G1134-G1143 [PMID: 22997197 DOI: 10.1152/ajpgi.00321.2012]

129   **Zhang J**, Owen CR, Sanders MA, Turner JR, Basson MD. The motogenic effects of cyclic mechanical strain on intestinal epithelial monolayer wound closure are matrix dependent. *Gastroenterology* 2006; **131**: 1179-1189 [PMID: 17030187 DOI: 10.1053/j.gastro.2006.08.007]

130   **Komuro Y**, Ishihara K, Ohara S, Saigenji K, Hotta K. Effects of tetragastrin on mucus glycoprotein in rat gastric mucosal protection. *Gastroenterol Jpn* 1992; **27**: 597-603 [PMID: 1385248 DOI: 10.1007/BF02774973]

131   **Yoneda M**, Taché Y. Central thyrotropin-releasing factor analog prevents ethanol-induced gastric damage through prostaglandins in rats. *Gastroenterology* 1992; **102**: 1568-1574 [PMID: 1568566 DOI: 10.1016/0016-5085(92)91715-G]

132   **Takeuchi K**, Nishiwaki H, Okada M, Okabe S. Mucosal protective action of histamine against gastric lesions induced by HCl in rats: importance of antigastric motor activity mediated by H2-receptors. *J Pharmacol Exp Ther* 1988; **245**: 632-638 [PMID: 2966857]

133   **Tanaka S**, Akiba Y, Kaunitz JD. Pentagastrin gastroprotection against acid is related to H2 receptor activation but not acid secretion. *Gut* 1998; **43**: 334-341 [PMID: 9863477 DOI: 10.1136/GUT.43.3.334]

134   **Konturek SJ**, Brzozowski T, Bielanski W, Schally AV. Role of endogenous gastrin in gastroprotection. *Eur J Pharmacol* 1995; **278**: 203-212 [PMID: 7589156 DOI: 10.1016/0014-2999(95)00120-A]

135   **Kivilaakso E**, Fromm D, Silen W. Effect of the acid secretory state on intramural pH of rabbit gastric mucosa. *Gastroenterology* 1978; **75**: 641-648 [PMID: 30670 DOI: 10.1016/S0016-5085(19)31673-7]

136   **Smith P**, O'Brien P, Fromm D, Silen W. Secretory state of gastric mucosa and resistance to injury by exogenous acid. *Am J Surg* 1977; **133**: 81-85 [PMID: 13668 DOI: 10.1016/0002-9610(77)90198-2]

137   **Tanaka S**, Taché Y, Kaneko H, Guth PH, Kaunitz JD. Central vagal activation increases mucus gel thickness and surface cell intracellular pH in rat stomach. *Gastroenterology* 1997; **112**: 409-417 [PMID: 9024294 DOI: 10.1053/GAST.1997.V112.PM9024294]

138   **Ciacci C**, Lind SE, Podolsky DK. Transforming growth factor beta regulation of migration in wounded rat intestinal epithelial monolayers. *Gastroenterology* 1993; **105**: 93-101 [PMID: 8514065 DOI: 10.1016/0016-5085(93)90014-4]

139   **Dignass AU**, Podolsky DK. Interleukin 2 modulates intestinal epithelial cell function in vitro. *Exp Cell Res* 1996; **225**: 422-429 [PMID: 8660931 DOI: 10.1006/EXCR.1996.0193]

140   **Dise RS**, Frey MR, Whitehead RH, Polk DB. Epidermal growth factor stimulates Rac activation through Src and phosphatidylinositol 3-kinase to promote colonic epithelial cell migration. *Am J Physiol Gastrointest Liver Physiol* 2008; **294**: G276-G285 [PMID: 17991704 DOI: 10.1152/AJPGI.00340.2007]

141   **Jones MK**, Kawanaka H, Baatar D, Szabó IL, Tsugawa K, Pai R, Koh GY, Kim I, Sarfeh IJ, Tarnawski AS. Gene therapy for gastric ulcers with single local injection of naked DNA encoding VEGF and angiopoietin-1. *Gastroenterology* 2001; **121**: 1040-1047 [PMID: 11677194 DOI: 10.1053/GAST.2001.29308]

142   **Ferrara N**. The role of VEGF in the regulation of physiological and pathological angiogenesis. *EXS* 2005; 209-231 [PMID: 15617481 DOI: 10.1007/3-7643-7311-3_15]

143   **Szabo S**, Folkman J, Vattay P, Morales RE, Pinkus GS, Kato K. Accelerated healing of duodenal ulcers by oral administration of a mutein of basic fibroblast growth factor in rats. *Gastroenterology* 1994; **106**: 1106-1111 [PMID: 8143978 DOI: 10.1016/0016-5085(94)90773-0]

144   **Tarnawski AS**, Ahluwalia A. The Critical Role of Growth Factors in Gastric Ulcer Healing: The Cellular and Molecular Mechanisms and Potential Clinical Implications. *Cells* 2021; **10** [PMID: 34440733 DOI: 10.3390/CELLS10081964]

145   **Ebner R**, Derynck R. Epidermal growth factor and transforming growth factor-alpha: differential intracellular routing and processing of ligand-receptor complexes. *Cell Regul* 1991; **2**: 599-612 [PMID: 1777504 DOI: 10.1091/MBC.2.8.599]

146   **Ishikawa S**, Cepinskas G, Specian RD, Itoh M, Kvietys PR. Epidermal growth factor attenuates jejunal mucosal injury induced by oleic acid: role of mucus. *Am J Physiol* 1994; **267**: G1067-G1077 [PMID: 7810653 DOI: 10.1152/AJPGI.1994.267.6.G1067]

147   **Sarosiek J**, Bilski J, Murty VL, Slomiany A, Slomiany BL. Role of salivary epidermal growth factor in the maintenance of physicochemical characteristics of oral and gastric mucosal mucus coat. *Biochem Biophys Res Commun* 1988; **152**: 1421-1427 [PMID: 3259876 DOI: 10.1016/S0006-291X(88)80444-3]

148   **Kelly SM**, Hunter JO. Epidermal growth factor stimulates synthesis and secretion of mucus glycoproteins in human gastric mucosa. *Clin Sci (Lond)* 1990; **79**: 425-427 [PMID: 2174308 DOI: 10.1042/CS0790425]

149   **Procaccino F**, Reinshagen M, Hoffmann P, Zeeh JM, Lakshmanan J, McRoberts JA, Patel A, French S, Eysselein VE. Protective effect of epidermal growth factor in an experimental model of colitis in rats. *Gastroenterology* 1994; **107**: 12-17 [PMID: 8020654 DOI: 10.1016/0016-5085(94)90055-8]

150   **Riegler M**, Sedivy R, Sogukoglu T, Castagliuolo I, Pothoulakis C, Cosentini E, Bischof G, Hamilton G, Teleky B, Feil W, Lamont JT, Wenzl E. Epidermal growth factor attenuates Clostridium difficile toxin A- and B-induced damage of human colonic mucosa. *Am J Physiol* 1997; **273**: G1014-G1022 [PMID: 9374697 DOI: 10.1152/ajpgi.1997.273.5.G1014]

151   **Hui WM**, Chen BW, Kung AW, Cho CH, Luk CT, Lam SK. Effect of epidermal growth factor on gastric blood flow in rats: possible role in mucosal protection. *Gastroenterology* 1993; **104**: 1605-1610 [PMID: 8500716 DOI: 10.1016/0016-5085(93)90635-P]

152   **Konturek PK**, Brzozowski T, Konturek SJ, Dembiński A. Role of epidermal growth factor, prostaglandin, and sulfhydryls in stress-induced gastric lesions. *Gastroenterology* 1990; **99**: 1607-1615 [PMID: 2227276 DOI: 10.1016/0016-5085(90)90464-C]

153   **Sakamoto T**, Swierczek JS, Ogden WD, Thompson JC. Cytoprotective effect of pentagastrin and epidermal growth factor

on stress ulcer formation. Possible role of somatostatin. *Ann Surg* 1985; **201**: 290-295 [PMID: 2858183 DOI: 10.1097/00000658-198503000-00005]

154 **Tarnawski AS**, Jones MK. The role of epidermal growth factor (EGF) and its receptor in mucosal protection, adaptation to injury, and ulcer healing: involvement of EGF-R signal transduction pathways. *J Clin Gastroenterol* 1998; **27** Suppl 1: S12-S20 [PMID: 9872493 DOI: 10.1097/00004836-199800001-00004]

155 **Kirkegaard P**, Olsen PS, Poulsen SS, Nexø E. Epidermal growth factor inhibits cysteamine-induced duodenal ulcers. *Gastroenterology* 1983; **85**: 1277-1283 [PMID: 6605273 DOI: 10.1016/S0016-5085(83)80007-9]

156 **Kosone T**, Takagi H, Kakizaki S, Sohara N, Horiguchi N, Sato K, Yoneda M, Takeuchi T, Mori M. Integrative roles of transforming growth factor-alpha in the cytoprotection mechanisms of gastric mucosal injury. *BMC Gastroenterol* 2006; **6**: 22 [PMID: 16879752 DOI: 10.1186/1471-230X-6-22]

157 **Konturek SJ**, Brzozowski T, Majka J, Dembinski A, Slomiany A, Slomiany BL. Transforming growth factor alpha and epidermal growth factor in protection and healing of gastric mucosal injury. *Scand J Gastroenterol* 1992; **27**: 649-655 [PMID: 1439546 DOI: 10.3109/00365529209000134]

158 **Kokoska ER**, Wolff AB, Smith GS, Miller TA. Epidermal growth factor-induced cytoprotection in human intestinal cells involves intracellular calcium signaling. *J Surg Res* 2000; **88**: 97-103 [PMID: 10644473 DOI: 10.1006/JSRE.1999.5740]

159 **Nylander-Koski O**, Mustonen H, Puolakkainen P, Kiviluoto T, Kivilaakso E. Epidermal growth factor enhances intracellular pH regulation *via* calcium signaling in acid-exposed primary cultured rabbit gastric epithelial cells. *Dig Dis Sci* 2006; **51**: 1322-1330 [PMID: 16832619 DOI: 10.1007/S10620-006-9075-7]

160 **Tarnawski AS**, Jones MK, Ahluwalia A. Dedifferentiation and reprogramming of epithelial cells during gastric ulcer healing is triggered by hypoxia and a well-coordinated, sequential activation of EGFR signaling: cross talk with IGF1 and COX2. *Gastroenterology* 2021; **160**: 77-78 [DOI: 10.1016/S0016-5085(21)00932-X]

161 **Brzozowski T**, Konturek PC, Konturek SJ, Schuppan D, Drozdowicz D, Kwiecień S, Majka J, Nakamura T, Hahn E. Effect of local application of growth factors on gastric ulcer healing and mucosal expression of cyclooxygenase-1 and -2. *Digestion* 2001; **64**: 15-29 [PMID: 11549833 DOI: 10.1159/000048835]

162 **Eberhart CE**, Dubois RN. Eicosanoids and the gastrointestinal tract. *Gastroenterology* 1995; **109**: 285-301 [PMID: 7797026 DOI: 10.1016/0016-5085(95)90296-1]

163 **Jones MK**, Sasaki E, Halter F, Pai R, Nakamura T, Arakawa T, Kuroki T, Tarnawski AS. HGF triggers activation of the COX-2 gene in rat gastric epithelial cells: action mediated through the ERK2 signaling pathway. *FASEB J* 1999; **13**: 2186-2194 [PMID: 10593866 DOI: 10.1096/FASEBJ.13.15.2186]

164 **Babyatsky MW**, deBeaumont M, Thim L, Podolsky DK. Oral trefoil peptides protect against ethanol- and indomethacin-induced gastric injury in rats. *Gastroenterology* 1996; **110**: 489-497 [PMID: 8566596 DOI: 10.1053/GAST.1996.V110.PM8566596]

165 **FitzGerald AJ**, Pu M, Marchbank T, Westley BR, May FE, Boyle J, Yadollahi-Farsani M, Ghosh S, Playford RJ. Synergistic effects of systemic trefoil factor family 1 (TFF1) peptide and epidermal growth factor in a rat model of colitis. *Peptides* 2004; **25**: 793-801 [PMID: 15177874 DOI: 10.1016/J.PEPTIDES.2003.12.022]

166 **Vandenbroucke K**, Hans W, Van Huysse J, Neirynck S, Demetter P, Remaut E, Rottiers P, Steidler L. Active delivery of trefoil factors by genetically modified Lactococcus lactis prevents and heals acute colitis in mice. *Gastroenterology* 2004; **127**: 502-513 [PMID: 15300583 DOI: 10.1053/J.GASTRO.2004.05.020]

167 **Thim L**, Madsen F, Poulsen SS. Effect of trefoil factors on the viscoelastic properties of mucus gels. *Eur J Clin Invest* 2002; **32**: 519-527 [PMID: 12153553 DOI: 10.1046/J.1365-2362.2002.01014.X]

168 **Bastholm SK**, Samson MH, Becher N, Hansen LK, Stubbe PR, Chronakis IS, Nexo E, Uldbjerg N. Trefoil factor peptide 3 is positively correlated with the viscoelastic properties of the cervical mucus plug. *Acta Obstet Gynecol Scand* 2017; **96**: 47-52 [PMID: 27731893 DOI: 10.1111/aogs.13038]

169 **Wong WM**, Poulsom R, Wright NA. Trefoil peptides. *Gut* 1999; **44**: 890-895 [PMID: 10323896 DOI: 10.1136/GUT.44.6.890]

170 **Xue L**, Aihara E, Podolsky DK, Wang TC, Montrose MH. In vivo action of trefoil factor 2 (TFF2) to speed gastric repair is independent of cyclooxygenase. *Gut* 2010; **59**: 1184-1191 [PMID: 20587547 DOI: 10.1136/gut.2009.205625]

171 **Xue L**, Aihara E, Wang TC, Montrose MH. Trefoil factor 2 requires Na/H exchanger 2 activity to enhance mouse gastric epithelial repair. *J Biol Chem* 2011; **286**: 38375-38382 [PMID: 21900251 DOI: 10.1074/jbc.M111.268219]

172 **McBerry C**, Egan CE, Rani R, Yang Y, Wu D, Boespflug N, Boon L, Butcher B, Mirpuri J, Hogan SP, Denkers EY, Aliberti J, Herbert DR. Trefoil factor 2 negatively regulates type 1 immunity against Toxoplasma gondii. *J Immunol* 2012; **189**: 3078-3084 [PMID: 22896633 DOI: 10.4049/jimmunol.1103374]

173 **Järvå MA**, Lingford JP, John A, Soler NM, Scott NE, Goddard-Borger ED. Trefoil factors share a lectin activity that defines their role in mucus. *Nat Commun* 2020; **11**: 2265 [PMID: 32404934 DOI: 10.1038/s41467-020-16223-7]

174 **Newton JL**, Allen A, Westley BR, May FE. The human trefoil peptide, TFF1, is present in different molecular forms that are intimately associated with mucus in normal stomach. *Gut* 2000; **46**: 312-320 [PMID: 10673290 DOI: 10.1136/GUT.46.3.312]

175 **Aihara E**, Engevik KA, Montrose MH. Trefoil Factor Peptides and Gastrointestinal Function. *Annu Rev Physiol* 2017; **79**: 357-380 [PMID: 27992733 DOI: 10.1146/annurev-physiol-021115-105447]

176 **Braga Emidio N**, Brierley SM, Schroeder CI, Muttenthaler M. Structure, Function, and Therapeutic Potential of the Trefoil Factor Family in the Gastrointestinal Tract. *ACS Pharmacol Transl Sci* 2020; **3**: 583-597 [PMID: 32832864 DOI: 10.1021/acsptsci.0c00023]

177 **Farrell JJ**, Taupin D, Koh TJ, Chen D, Zhao CM, Podolsky DK, Wang TC. TFF2/SP-deficient mice show decreased gastric proliferation, increased acid secretion, and increased susceptibility to NSAID injury. *J Clin Invest* 2002; **109**: 193-204 [PMID: 11805131 DOI: 10.1172/JCI12529]

178 **Belle NM**, Ji Y, Herbine K, Wei Y, Park J, Zullo K, Hung LY, Srivatsa S, Young T, Oniskey T, Pastore C, Nieves W, Somsouk M, Herbert DR. TFF3 interacts with LINGO2 to regulate EGFR activation for protection against colitis and gastrointestinal helminths. *Nat Commun* 2019; **10**: 4408 [PMID: 31562318 DOI: 10.1038/s41467-019-12315-1]

179 **Hoffmann W**. Trefoil Factor Family (TFF) Peptides and Their Links to Inflammation: A Re-evaluation and New Medical

Perspectives. *Int J Mol Sci* 2021; **22** [PMID: 34066339 DOI: 10.3390/IJMS22094909]

180   **Dieckow J**, Brandt W, Hattermann K, Schob S, Schulze U, Mentlein R, Ackermann P, Sel S, Paulsen FP. CXCR4 and CXCR7 Mediate TFF3-Induced Cell Migration Independently From the ERK1/2 Signaling Pathway. *Invest Ophthalmol Vis Sci* 2016; **57**: 56-65 [PMID: 26780310 DOI: 10.1167/iovs.15-18129]

181   **Orime K**, Shirakawa J, Togashi Y, Tajima K, Inoue H, Ito Y, Sato K, Nakamura A, Aoki K, Goshima Y, Terauchi Y. Trefoil factor 2 promotes cell proliferation in pancreatic β-cells through CXCR-4-mediated ERK1/2 phosphorylation. *Endocrinology* 2013; **154**: 54-64 [PMID: 23183167 DOI: 10.1210/en.2012-1814]

182   **Taupin D**, Wu DC, Jeon WK, Devaney K, Wang TC, Podolsky DK. The trefoil gene family are coordinately expressed immediate-early genes: EGF receptor- and MAP kinase-dependent interregulation. *J Clin Invest* 1999; **103**: R31-R38 [PMID: 10225980 DOI: 10.1172/JCI3304]

183   **Sun Z**, Liu H, Yang Z, Shao D, Zhang W, Ren Y, Sun B, Lin J, Xu M, Nie S. Intestinal trefoil factor activates the PI3K/Akt signaling pathway to protect gastric mucosal epithelium from damage. *Int J Oncol* 2014; **45**: 1123-1132 [PMID: 24990304 DOI: 10.3892/ijo.2014.2527]

184   **Dubeykovskaya Z**, Dubeykovskiy A, Solal-Cohen J, Wang TC. Secreted trefoil factor 2 activates the CXCR4 receptor in epithelial and lymphocytic cancer cell lines. *J Biol Chem* 2009; **284**: 3650-3662 [PMID: 19064997 DOI: 10.1074/jbc.M804935200]

185   **Zhang Y**, Yu G, Wang Y, Xiang Y, Gao Q, Jiang P, Zhang J, Lee W, Zhang Y. Activation of protease-activated receptor (PAR) 1 by frog trefoil factor (TFF) 2 and PAR4 by human TFF2. *Cell Mol Life Sci* 2011; **68**: 3771-3780 [PMID: 21461878 DOI: 10.1007/s00018-011-0678-6]

186   **Barrera GJ**, Tortolero GS. Trefoil factor 3 (TFF3) from human breast milk activates PAR-2 receptors, of the intestinal epithelial cells HT-29, regulating cytokines and defensins. *Bratisl Lek Listy* 2016; **117**: 332-339 [PMID: 27546365 DOI: 10.4149/BLL_2016_066]

187   **McKenzie C**, Thim L, Parsons ME. Topical and intravenous administration of trefoil factors protect the gastric mucosa from ethanol-induced injury in the rat. *Aliment Pharmacol Ther* 2000; **14**: 1033-1040 [PMID: 10930897 DOI: 10.1046/J.1365-2036.2000.00796.X]

188   **Playford RJ**, Marchbank T, Goodlad RA, Chinery RA, Poulsom R, Hanby AM. Transgenic mice that overexpress the human trefoil peptide pS2 have an increased resistance to intestinal damage. *Proc Natl Acad Sci USA* 1996; **93**: 2137-2142 [PMID: 8700898 DOI: 10.1073/PNAS.93.5.2137]

189   **Mashimo H**, Wu DC, Podolsky DK, Fishman MC. Impaired defense of intestinal mucosa in mice lacking intestinal trefoil factor. *Science* 1996; **274**: 262-265 [PMID: 8824194 DOI: 10.1126/SCIENCE.274.5285.262]

190   **Babyatsky MW**, Rossiter G, Podolsky DK. Expression of transforming growth factors alpha and beta in colonic mucosa in inflammatory bowel disease. *Gastroenterology* 1996; **110**: 975-984 [PMID: 8613031 DOI: 10.1053/GAST.1996.V110.PM8613031]

191   **Maric I**, Poljak L, Zoricic S, Bobinac D, Bosukonda D, Sampath KT, Vukicevic S. Bone morphogenetic protein-7 reduces the severity of colon tissue damage and accelerates the healing of inflammatory bowel disease in rats. *J Cell Physiol* 2003; **196**: 258-264 [PMID: 12811818 DOI: 10.1002/JCP.10275]

192   **Sommer K**, Wiendl M, Müller TM, Heidbreder K, Voskens C, Neurath MF, Zundler S. Intestinal Mucosal Wound Healing and Barrier Integrity in IBD-Crosstalk and Trafficking of Cellular Players. *Front Med (Lausanne)* 2021; **8**: 643973 [PMID: 33834033 DOI: 10.3389/fmed.2021.643973]

193   **Bulut K**, Pennartz C, Felderbauer P, Ansorge N, Banasch M, Schmitz F, Schmidt WE, Hoffmann P. Vascular endothelial growth factor (VEGF164) ameliorates intestinal epithelial injury in vitro in IEC-18 and Caco-2 monolayers *via* induction of TGF-beta release from epithelial cells. *Scand J Gastroenterol* 2006; **41**: 687-692 [PMID: 16716967 DOI: 10.1080/00365520500408634]

194   **Ahluwalia A**, Jones MK, Brzozowski T, Tarnawski AS. Nerve growth factor is critical requirement for in vitro angiogenesis in gastric endothelial cells. *Am J Physiol Gastrointest Liver Physiol* 2016; **311**: G981-G987 [PMID: 27742705 DOI: 10.1152/ajpgi.00334.2016]

195   **Velazquez OC**. Angiogenesis and vasculogenesis: inducing the growth of new blood vessels and wound healing by stimulation of bone marrow-derived progenitor cell mobilization and homing. *J Vasc Surg* 2007; **45** Suppl A: A39-A47 [PMID: 17544023 DOI: 10.1016/J.JVS.2007.02.068]

196   **Chai J**, Baatar D, Tarnawski A. Serum response factor promotes re-epithelialization and muscular structure restoration during gastric ulcer healing. *Gastroenterology* 2004; **126**: 1809-1818 [PMID: 15188176 DOI: 10.1053/J.GASTRO.2004.03.021]

197   **Ahluwalia A**, Jones MK, Brzozowska I, Tarnawski AS. In vitro model of vasculo-angiogenesis: demonstration that bone marrow derived endothelial progenitor cells form new hybrid capillary blood vessels jointly with gastric endothelial cells. *J Physiol Pharmacol* 2017; **68**: 841-846 [PMID: 29550796]

198   **Neurath MF**. Cytokines in inflammatory bowel disease. *Nat Rev Immunol* 2014; **14**: 329-342 [PMID: 24751956 DOI: 10.1038/nri3661]

199   **Leppkes M**, Becker C, Ivanov II, Hirth S, Wirtz S, Neufert C, Pouly S, Murphy AJ, Valenzuela DM, Yancopoulos GD, Becher B, Littman DR, Neurath MF. RORgamma-expressing Th17 cells induce murine chronic intestinal inflammation *via* redundant effects of IL-17A and IL-17F. *Gastroenterology* 2009; **136**: 257-267 [PMID: 18992745 DOI: 10.1053/j.gastro.2008.10.018]

200   **Hueber W**, Sands BE, Lewitzky S, Vandemeulebroecke M, Reinisch W, Higgins PD, Wehkamp J, Feagan BG, Yao MD, Karczewski M, Karczewski J, Pezous N, Bek S, Bruin G, Mellgard B, Berger C, Londei M, Bertolino AP, Tougas G, Travis SP; Secukinumab in Crohn's Disease Study Group. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. *Gut* 2012; **61**: 1693-1700 [PMID: 22595313 DOI: 10.1136/gutjnl-2011-301668]

201   **Rosen MJ**, Frey MR, Washington MK, Chaturvedi R, Kuhnhein LA, Matta P, Revetta FL, Wilson KT, Polk DB. STAT6 activation in ulcerative colitis: a new target for prevention of IL-13-induced colon epithelial cell dysfunction. *Inflamm Bowel Dis* 2011; **17**: 2224-2234 [PMID: 21308881 DOI: 10.1002/ibd.21628]

202   **Heller F**, Fuss IJ, Nieuwenhuis EE, Blumberg RS, Strober W. Oxazolone colitis, a Th2 colitis model resembling ulcerative colitis, is mediated by IL-13-producing NK-T cells. *Immunity* 2002; **17**: 629-638 [PMID: 12433369 DOI: 10.1016/S1074-7613(02)00453-3]

203   **Weigmann B**, Lehr HA, Yancopoulos G, Valenzuela D, Murphy A, Stevens S, Schmidt J, Galle PR, Rose-John S, Neurath MF. The transcription factor NFATc2 controls IL-6-dependent T cell activation in experimental colitis. *J Exp Med* 2008; **205**: 2099-2110 [PMID: 18710929 DOI: 10.1084/jem.20072484]

204   **Hoving JC**. Targeting IL-13 as a Host-Directed Therapy Against Ulcerative Colitis. *Front Cell Infect Microbiol* 2018; **8**: 395 [PMID: 30460209 DOI: 10.3389/fcimb.2018.00395]

205   **Tilg H**, Kaser A. Failure of interleukin 13 blockade in ulcerative colitis. *Gut* 2015; **64**: 857-858 [PMID: 25804632 DOI: 10.1136/gutjnl-2015-309464]

206   **Ouyang W**, Rutz S, Crellin NK, Valdez PA, Hymowitz SG. Regulation and functions of the IL-10 family of cytokines in inflammation and disease. *Annu Rev Immunol* 2011; **29**: 71-109 [PMID: 21166540 DOI: 10.1146/annurev-immunol-031210-101312]

207   **Lindsay J**, Van Montfrans C, Brennan F, Van Deventer S, Drillenburg P, Hodgson H, Te Velde A, Sol Rodriguez Pena M. IL-10 gene therapy prevents TNBS-induced colitis. *Gene Ther* 2002; **9**: 1715-1721 [PMID: 12457286 DOI: 10.1038/sj.gt.3301841]

208   **Li MC**, He SH. IL-10 and its related cytokines for treatment of inflammatory bowel disease. *World J Gastroenterol* 2004; **10**: 620-625 [PMID: 14991925 DOI: 10.3748/WJG.V10.I5.620]

209   **Fedorak RN**, Gangl A, Elson CO, Rutgeerts P, Schreiber S, Wild G, Hanauer SB, Kilian A, Cohard M, LeBeaut A, Feagan B. Recombinant human interleukin 10 in the treatment of patients with mild to moderately active Crohn's disease. The Interleukin 10 Inflammatory Bowel Disease Cooperative Study Group. *Gastroenterology* 2000; **119**: 1473-1482 [PMID: 11113068 DOI: 10.1053/GAST.2000.20229]

210   **Wei HX**, Wang B, Li B. IL-10 and IL-22 in Mucosal Immunity: Driving Protection and Pathology. *Front Immunol* 2020; **11**: 1315 [PMID: 32670290 DOI: 10.3389/fimmu.2020.01315]

211   **Zheng Y**, Danilenko DM, Valdez P, Kasman I, Eastham-Anderson J, Wu J, Ouyang W. Interleukin-22, a T(H)17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. *Nature* 2007; **445**: 648-651 [PMID: 17187052 DOI: 10.1038/NATURE05505]

212   **Wolk K**, Witte E, Hoffmann U, Doecke WD, Endesfelder S, Asadullah K, Sterry W, Volk HD, Wittig BM, Sabat R. IL-22 induces lipopolysaccharide-binding protein in hepatocytes: a potential systemic role of IL-22 in Crohn's disease. *J Immunol* 2007; **178**: 5973-5981 [PMID: 17442982 DOI: 10.4049/JIMMUNOL.178.9.5973]

213   **Pickert G**, Neufert C, Leppkes M, Zheng Y, Wittkopf N, Warntjen M, Lehr HA, Hirth S, Weigmann B, Wirtz S, Ouyang W, Neurath MF, Becker C. STAT3 links IL-22 signaling in intestinal epithelial cells to mucosal wound healing. *J Exp Med* 2009; **206**: 1465-1472 [PMID: 19564350 DOI: 10.1084/jem.20082683]

214   **Gao B**, Xiang X. Interleukin-22 from bench to bedside: a promising drug for epithelial repair. *Cell Mol Immunol* 2019; **16**: 666-667 [PMID: 29921965 DOI: 10.1038/s41423-018-0055-6]

215   **Lee DW**, Zhong S, Pai R, Rae J, Sukumaran S, Stefanich EG, Lutman J, Doudement E, Wang X, Harder B, Lekkerkerker A, Herman A, Ouyang W, Danilenko DM. Nonclinical safety assessment of a human interleukin-22FC IG fusion protein demonstrates in vitro to in vivo and cross-species translatability. *Pharmacol Res Perspect* 2018; **6**: e00434 [PMID: 30464842 DOI: 10.1002/prp2.434]

216   **Zheng Y**, Valdez PA, Danilenko DM, Hu Y, Sa SM, Gong Q, Abbas AR, Modrusan Z, Ghilardi N, de Sauvage FJ, Ouyang W. Interleukin-22 mediates early host defense against attaching and effacing bacterial pathogens. *Nat Med* 2008; **14**: 282-289 [PMID: 18264109 DOI: 10.1038/nm1720]

217   **Aujla SJ**, Chan YR, Zheng M, Fei M, Askew DJ, Pociask DA, Reinhart TA, McAllister F, Edeal J, Gaus K, Husain S, Kreindler JL, Dubin PJ, Pilewski JM, Myerburg MM, Mason CA, Iwakura Y, Kolls JK. IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia. *Nat Med* 2008; **14**: 275-281 [PMID: 18264110 DOI: 10.1038/nm1710]

218   **Sugimoto K**, Ogawa A, Mizoguchi E, Shimomura Y, Andoh A, Bhan AK, Blumberg RS, Xavier RJ, Mizoguchi A. IL-22 ameliorates intestinal inflammation in a mouse model of ulcerative colitis. *J Clin Invest* 2008; **118**: 534-544 [PMID: 18172556 DOI: 10.1172/JCI33194]

219   **Eken A**, Singh AK, Treuting PM, Oukka M. IL-23R+ innate lymphoid cells induce colitis *via* interleukin-22-dependent mechanism. *Mucosal Immunol* 2014; **7**: 143-154 [PMID: 23715173 DOI: 10.1038/mi.2013.33]

220   **Stefanich EG**, Rae J, Sukumaran S, Lutman J, Lekkerkerker A, Ouyang W, Wang X, Lee D, Danilenko DM, Diehl L, Loyet KM, Herman A. Pre-clinical and translational pharmacology of a human interleukin-22 IgG fusion protein for potential treatment of infectious or inflammatory diseases. *Biochem Pharmacol* 2018; **152**: 224-235 [PMID: 29608910 DOI: 10.1016/j.bcp.2018.03.031]

221   **Rothenberg ME**, Wang Y, Lekkerkerker A, Danilenko DM, Maciuca R, Erickson R, Herman A, Stefanich E, Lu TT. Randomized Phase I Healthy Volunteer Study of UTTR1147A (IL-22Fc): A Potential Therapy for Epithelial Injury. *Clin Pharmacol Ther* 2019; **105**: 177-189 [PMID: 29952004 DOI: 10.1002/cpt.1164]

222   **Genentech**, Inc.   An Extension Study to Evaluate the Long-Term Safety and Tolerability of UTTR1147A in Participants With Moderate to Severe Ulcerative Colitis or Crohn's Disease. ClinicalTrials.gov Identifier: NCT03650413 Available from: https://clinicaltrials.gov/ct2/show/NCT03650413

223   **Canani RB**, Costanzo MD, Leone L, Pedata M, Meli R, Calignano A. Potential beneficial effects of butyrate in intestinal and extraintestinal diseases. *World J Gastroenterol* 2011; **17**: 1519-1528 [PMID: 21472114 DOI: 10.3748/wjg.v17.i12.1519]

224   **Rao JN**, Wang JY.   Regulation of Gastrointestinal Mucosal Growth. In: Integrated Systems Physiology: from Molecule to Function to Disease. San Rafael (CA): Morgan & Claypool Life Sciences; 2010 [PMID: 21634069 DOI: 10.4199/C00028ED1V01Y201103ISP015]

225   **Hamer HM**, Jonkers D, Venema K, Vanhoutvin S, Troost FJ, Brummer RJ. Review article: the role of butyrate on colonic function. *Aliment Pharmacol Ther* 2008; **27**: 104-119 [PMID: 17973645 DOI: 10.1111/J.1365-2036.2007.03562.X]

226   **Bedford A**, Gong J. Implications of butyrate and its derivatives for gut health and animal production. *Anim Nutr* 2018; **4**: 151-159 [PMID: 30140754 DOI: 10.1016/j.aninu.2017.08.010]

227   **Okumura R**, Takeda K. Roles of intestinal epithelial cells in the maintenance of gut homeostasis. *Exp Mol Med* 2017; **49**: e338 [PMID: 28546564 DOI: 10.1038/emm.2017.20]

228   **Park JH**, Kotani T, Konno T, Setiawan J, Kitamura Y, Imada S, Usui Y, Hatano N, Shinohara M, Saito Y, Murata Y, Matozaki T. Promotion of Intestinal Epithelial Cell Turnover by Commensal Bacteria: Role of Short-Chain Fatty Acids. *PLoS One* 2016; **11**: e0156334 [PMID: 27232601 DOI: 10.1371/journal.pone.0156334]

229   **Parada Venegas D**, De la Fuente MK, Landskron G, González MJ, Quera R, Dijkstra G, Harmsen HJM, Faber KN, Hermoso MA. Short Chain Fatty Acids (SCFAs)-Mediated Gut Epithelial and Immune Regulation and Its Relevance for Inflammatory Bowel Diseases. *Front Immunol* 2019; **10**: 277 [PMID: 30915065 DOI: 10.3389/fimmu.2019.00277]

230   **Bilotta AJ**, Ma C, Yang W, Yu Y, Zhao X, Zhou Z, Yao S, Dann SM, Cong Y. Propionate Enhances Cell Speed and Persistence to Promote Intestinal Epithelial Turnover and Repair. *Cell Mol Gastroenterol Hepatol* 2021; **11**: 1023-1044 [PMID: 33238220 DOI: 10.1016/j.jcmgh.2020.11.011]

231   **Basson MD**, Liu YW, Hanly AM, Emenaker NJ, Shenoy SG, Gould Rothberg BE. Identification and comparative analysis of human colonocyte short-chain fatty acid response genes. *J Gastrointest Surg* 2000; **4**: 501-512 [PMID: 11077326 DOI: 10.1016/S1091-255X(00)80093-1]

232   **Basson MD**, Turowski GA, Rashid Z, Hong F, Madri JA. Regulation of human colonic cell line proliferation and phenotype by sodium butyrate. *Dig Dis Sci* 1996; **41**: 1989-1993 [PMID: 8888712 DOI: 10.1007/BF02093601]

233   **Basson MD**, Emenaker NJ, Hong F. Differential modulation of human (Caco-2) colon cancer cell line phenotype by short chain fatty acids. *Proc Soc Exp Biol Med* 1998; **217**: 476-483 [PMID: 9521097 DOI: 10.3181/00379727-217-44261]

234   **Gamet L**, Daviaud D, Denis-Pouxviel C, Remesy C, Murat JC. Effects of short-chain fatty acids on growth and differentiation of the human colon-cancer cell line HT29. *Int J Cancer* 1992; **52**: 286-289 [PMID: 1521915 DOI: 10.1002/IJC.2910520222]

235   **Dyson JE**, Daniel J, Surrey CR. The effect of sodium butyrate on the growth characteristics of human cervix tumour cells. *Br J Cancer* 1992; **65**: 803-808 [PMID: 1377482 DOI: 10.1038/BJC.1992.172]

236   **Mortensen FV**, Nielsen H, Mulvany MJ, Hessov I. Short chain fatty acids dilate isolated human colonic resistance arteries. *Gut* 1990; **31**: 1391-1394 [PMID: 2265780 DOI: 10.1136/GUT.31.12.1391]

237   **Mortensen FV**, Hessov I, Birke H, Korsgaard N, Nielsen H. Microcirculatory and trophic effects of short chain fatty acids in the human rectum after Hartmann's procedure. *Br J Surg* 1991; **78**: 1208-1211 [PMID: 1958986 DOI: 10.1002/BJS.1800781019]

238   **Peng L**, He Z, Chen W, Holzman IR, Lin J. Effects of butyrate on intestinal barrier function in a Caco-2 cell monolayer model of intestinal barrier. *Pediatr Res* 2007; **61**: 37-41 [PMID: 17211138 DOI: 10.1203/01.pdr.0000250014.92242.f3]

239   **Suzuki T**, Yoshida S, Hara H. Physiological concentrations of short-chain fatty acids immediately suppress colonic epithelial permeability. *Br J Nutr* 2008; **100**: 297-305 [PMID: 18346306 DOI: 10.1017/S0007114508888733]

240   **Terzi C**, Sevinç AI, Koçdor H, Oktay G, Alanyali H, Küpelioğlu A, Ergör G, Füzün M. Improvement of colonic healing by preoperative rectal irrigation with short-chain fatty acids in rats given radiotherapy. *Dis Colon Rectum* 2004; **47**: 2184-2194 [PMID: 15657672 DOI: 10.1007/S10350-004-0724-7]

241   **Elamin EE**, Masclee AA, Dekker J, Pieters HJ, Jonkers DM. Short-chain fatty acids activate AMP-activated protein kinase and ameliorate ethanol-induced intestinal barrier dysfunction in Caco-2 cell monolayers. *J Nutr* 2013; **143**: 1872-1881 [PMID: 24132573 DOI: 10.3945/jn.113.179549]

242   **Peng L**, Li ZR, Green RS, Holzman IR, Lin J. Butyrate enhances the intestinal barrier by facilitating tight junction assembly *via* activation of AMP-activated protein kinase in Caco-2 cell monolayers. *J Nutr* 2009; **139**: 1619-1625 [PMID: 19625695 DOI: 10.3945/jn.109.104638]

243   **Scheppach W**. Treatment of distal ulcerative colitis with short-chain fatty acid enemas. A placebo-controlled trial. German-Austrian SCFA Study Group. *Dig Dis Sci* 1996; **41**: 2254-2259 [PMID: 8943981 DOI: 10.1007/BF02071409]

244   **Duggan C**, Gannon J, Walker WA. Protective nutrients and functional foods for the gastrointestinal tract. *Am J Clin Nutr* 2002; **75**: 789-808 [PMID: 11976152 DOI: 10.1093/AJCN/75.5.789]

245   **Robinson EK**, Kelly DP, Mercer DW, Kozar RA. Differential effects of luminal arginine and glutamine on metalloproteinase production in the postischemic gut. *JPEN J Parenter Enteral Nutr* 2008; **32**: 433-438 [PMID: 18596315 DOI: 10.1177/0148607108319806]

246   **Kim MH**, Kim H. The Roles of Glutamine in the Intestine and Its Implication in Intestinal Diseases. *Int J Mol Sci* 2017; **18** [PMID: 28498331 DOI: 10.3390/ijms18051051]

247   **Fritz JH**. Arginine cools the inflamed gut. *Infect Immun* 2013; **81**: 3500-3502 [PMID: 23897606 DOI: 10.1128/IAI.00789-13]

248   **Matsui T**, Ichikawa H, Fujita T, Takemura S, Takagi T, Osada-Oka M, Minamiyama Y. Histidine and arginine modulate intestinal cell restitution *via* transforming growth factor-β$_1$. *Eur J Pharmacol* 2019; **850**: 35-42 [PMID: 30753862 DOI: 10.1016/j.ejphar.2019.02.006]

249   **Turowski GA**, Rashid Z, Hong F, Madri JA, Basson MD. Glutamine modulates phenotype and stimulates proliferation in human colon cancer cell lines. *Cancer Res* 1994; **54**: 5974-5980 [PMID: 7954430]

250   **Chen S**, Xia Y, Zhu G, Yan J, Tan C, Deng B, Deng J, Yin Y, Ren W. Glutamine supplementation improves intestinal cell proliferation and stem cell differentiation in weanling mice. *Food Nutr Res* 2018; **62** [PMID: 30083086 DOI: 10.29219/fnr.v62.1439]

251   **Ji FJ**, Wang LX, Yang HS, Hu A, Yin YL. Review: The roles and functions of glutamine on intestinal health and performance of weaning pigs. *Animal* 2019; **13**: 2727-2735 [PMID: 31407650 DOI: 10.1017/S1751731119001800]

252   **Swaid F**, Sukhotnik I, Matter I, Berkowitz D, Hadjittofi C, Pollak Y, Lavy A. Dietary glutamine supplementation prevents mucosal injury and modulates intestinal epithelial restitution following acetic acid induced intestinal injury in rats. *Nutr Metab (Lond)* 2013; **10**: 53 [PMID: 23919638 DOI: 10.1186/1743-7075-10-53]

253   **Tanaka T**, Morito K, Kinoshita M, Ohmoto M, Urikura M, Satouchi K, Tokumura A. Orally administered phosphatidic acids and lysophosphatidic acids ameliorate aspirin-induced stomach mucosal injury in mice. *Dig Dis Sci* 2013; **58**: 950-

958 [PMID: 23161268 DOI: 10.1007/s10620-012-2475-y]

254   **Hollander D**, Tarnawski A. Is there a role for dietary essential fatty acids in gastroduodenal mucosal protection? *J Clin Gastroenterol* 1991; **13** Suppl 1: S72-S74 [PMID: 1940200 DOI: 10.1097/00004836-199112001-00012]

255   **Bu HF**, Zuo XL, Wang X, Ensslin MA, Koti V, Hsueh W, Raymond AS, Shur BD, Tan XD. Milk fat globule-EGF factor 8/lactadherin plays a crucial role in maintenance and repair of murine intestinal epithelium. *J Clin Invest* 2007; **117**: 3673-3683 [PMID: 18008006 DOI: 10.1172/JCI31841]

256   **Hussey GS**, Keane TJ, Badylak SF. The extracellular matrix of the gastrointestinal tract: a regenerative medicine platform. *Nat Rev Gastroenterol Hepatol* 2017; **14**: 540-552 [PMID: 28698662 DOI: 10.1038/nrgastro.2017.76]

257   **Sonbol HS**. Extracellular Matrix Remodeling in Human Disease. *J Microsc Ultrastruct* 2018; **6**: 123-128 [PMID: 30221137 DOI: 10.4103/JMAU.JMAU_4_18]

258   **Olson AD**, Pysher T, Bienkowski RS. Organization of intestinal epithelial cells into multicellular structures requires laminin and functional actin microfilaments. *Exp Cell Res* 1991; **192**: 543-549 [PMID: 1988292 DOI: 10.1016/0014-4827(91)90074-5]

259   **Vachon PH**, Beaulieu JF. Extracellular heterotrimeric laminin promotes differentiation in human enterocytes. *Am J Physiol* 1995; **268**: G857-G867 [PMID: 7539221 DOI: 10.1152/AJPGI.1995.268.5.G857]

260   **Göke M**, Zuk A, Podolsky DK. Regulation and function of extracellular matrix intestinal epithelial restitution in vitro. *Am J Physiol* 1996; **271**: G729-G740 [PMID: 8944685 DOI: 10.1152/AJPGI.1996.271.5.G729]

261   **Zhang J**, Li W, Sanders MA, Sumpio BE, Panja A, Basson MD. Regulation of the intestinal epithelial response to cyclic strain by extracellular matrix proteins. *FASEB J* 2003; **17**: 926-928 [PMID: 12626437 DOI: 10.1096/FJ.02-0663FJE]

262   **Shimshoni E**, Yablecovitch D, Baram L, Dotan I, Sagi I. ECM remodelling in IBD: innocent bystander or partner in crime? *Gut* 2015; **64**: 367-372 [PMID: 25416065 DOI: 10.1136/gutjnl-2014-308048]

263   **Baugh MD**, Perry MJ, Hollander AP, Davies DR, Cross SS, Lobo AJ, Taylor CJ, Evans GS. Matrix metalloproteinase levels are elevated in inflammatory bowel disease. *Gastroenterology* 1999; **117**: 814-822 [PMID: 10500063 DOI: 10.1016/S0016-5085(99)70339-2]

264   **Kirkegaard T**, Hansen A, Bruun E, Brynskov J. Expression and localisation of matrix metalloproteinases and their natural inhibitors in fistulae of patients with Crohn's disease. *Gut* 2004; **53**: 701-709 [PMID: 15082589 DOI: 10.1136/GUT.2003.017442]

265   **Efsen E**, Saermark T, Hansen A, Bruun E, Brynskov J. Ramiprilate inhibits functional matrix metalloproteinase activity in Crohn's disease fistulas. *Basic Clin Pharmacol Toxicol* 2011; **109**: 208-216 [PMID: 21535409 DOI: 10.1111/j.1742-7843.2011.00713.x]

266   **Kofla-Dlubacz A**, Matusiewicz M, Krzystek-Korpacka M, Iwanczak B. Correlation of MMP-3 and MMP-9 with Crohn's disease activity in children. *Dig Dis Sci* 2012; **57**: 706-712 [PMID: 21997756 DOI: 10.1007/s10620-011-1936-z]

267   **Faubion WA Jr**, Fletcher JG, O'Byrne S, Feagan BG, de Villiers WJ, Salzberg B, Plevy S, Proctor DD, Valentine JF, Higgins PD, Harris JM, Diehl L, Wright L, Tew GW, Luca D, Basu K, Keir ME. EMerging BiomARKers in Inflammatory Bowel Disease (EMBARK) study identifies fecal calprotectin, serum MMP9, and serum IL-22 as a novel combination of biomarkers for Crohn's disease activity: role of cross-sectional imaging. *Am J Gastroenterol* 2013; **108**: 1891-1900 [PMID: 24126633 DOI: 10.1038/ajg.2013.354]

268   **Sela-Passwell N**, Kikkeri R, Dym O, Rozenberg H, Margalit R, Arad-Yellin R, Eisenstein M, Brenner O, Shoham T, Danon T, Shanzer A, Sagi I. Antibodies targeting the catalytic zinc complex of activated matrix metalloproteinases show therapeutic potential. *Nat Med* 2011; **18**: 143-147 [PMID: 22198278 DOI: 10.1038/nm.2582]

269   **Schreiber S**, Siegel CA, Friedenberg KA, Younes ZH, Seidler U, Bhandari BR, Wang K, Wendt E, McKevitt M, Zhao S, Sundy JS, Lee SD, Loftus EV. A Phase 2, Randomized, Placebo-Controlled Study Evaluating Matrix Metalloproteinase-9 Inhibitor, Andecaliximab, in Patients With Moderately to Severely Active Crohn's Disease. *J Crohns Colitis* 2018; **12**: 1014-1020 [PMID: 29846530 DOI: 10.1093/ecco-jcc/jjy070]

270   **Schreiber S**. Lack of Efficacy in Crohn's Disease Prompts Unplanned Interim Analysis and Termination of Study in Ulcerative Colitis. *J Crohns Colitis* 2020; **14**: 282 [PMID: 32037454 DOI: 10.1093/ecco-jcc/jjz142]

271   **Spiering D**, Hodgson L. Dynamics of the Rho-family small GTPases in actin regulation and motility. *Cell Adh Migr* 2011; **5**: 170-180 [PMID: 21178402 DOI: 10.4161/CAM.5.2.14403]

272   **Abreu-Blanco MT**, Watts JJ, Verboon JM, Parkhurst SM. Cytoskeleton responses in wound repair. *Cell Mol Life Sci* 2012; **69**: 2469-2483 [PMID: 22349211 DOI: 10.1007/s00018-012-0928-2]

273   **Chaturvedi LS**, Marsh HM, Basson MD. Role of RhoA and its effectors ROCK and mDia1 in the modulation of deformation-induced FAK, ERK, p38, and MLC motogenic signals in human Caco-2 intestinal epithelial cells. *Am J Physiol Cell Physiol* 2011; **301**: C1224-C1238 [PMID: 21849669 DOI: 10.1152/ajpcell.00518.2010]

274   **Kopecki Z**, Cowin AJ.   The Role of Actin Remodelling Proteins in Wound Healing and Tissue Regeneration. In: Wound Healing - New insights into Ancient Challenges. Intech Open, 2016 [DOI: 10.5772/64673]

275   **Heath JP**. Epithelial cell migration in the intestine. *Cell Biol Int* 1996; **20**: 139-146 [PMID: 8935158 DOI: 10.1006/CBIR.1996.0018]

276   **Tang DD**, Gerlach BD. The roles and regulation of the actin cytoskeleton, intermediate filaments and microtubules in smooth muscle cell migration. *Respir Res* 2017; **18**: 54 [PMID: 28390425 DOI: 10.1186/s12931-017-0544-7]

277   **Hohmann T**, Dehghani F. The Cytoskeleton-A Complex Interacting Meshwork. *Cells* 2019; **8** [PMID: 31003495 DOI: 10.3390/CELLS8040362]

278   **Etienne-Manneville S**. Actin and microtubules in cell motility: which one is in control? *Traffic* 2004; **5**: 470-477 [PMID: 15180824 DOI: 10.1111/J.1600-0854.2004.00196.X]

279   **Rottner K**, Schaks M. Assembling actin filaments for protrusion. *Curr Opin Cell Biol* 2019; **56**: 53-63 [PMID: 30278304 DOI: 10.1016/j.ceb.2018.09.004]

280   **Garcin C**, Straube A. Microtubules in cell migration. *Essays Biochem* 2019; **63**: 509-520 [PMID: 31358621 DOI: 10.1042/EBC20190016]

281   **Charafeddine RA**, Nosanchuk JD, Sharp DJ. Targeting Microtubules for Wound Repair. *Adv Wound Care (New Rochelle)* 2016; **5**: 444-454 [PMID: 27785378 DOI: 10.1089/WOUND.2015.0658]

282   **Campbell ID**, Ginsberg MH. The talin-tail interaction places integrin activation on FERM ground. *Trends Biochem Sci* 2004; **29**: 429-435 [PMID: 15362227 DOI: 10.1016/J.TIBS.2004.06.005]

283   **Bosanquet DC**, Ye L, Harding KG, Jiang WG. FERM family proteins and their importance in cellular movements and wound healing (review). *Int J Mol Med* 2014; **34**: 3-12 [PMID: 24820650 DOI: 10.3892/ijmm.2014.1775]

284   **Gurtner GC**, Wong VW. Filamin A Mediates Wound Closure by Promoting Elastic Deformation and Maintenance of Tension in the Collagen Matrix. *J Invest Dermatol* 2015; **135**: 2569-2571 [PMID: 26548489 DOI: 10.1038/jid.2015.327]

285   **Sun HQ**, Yamamoto M, Mejillano M, Yin HL. Gelsolin, a multifunctional actin regulatory protein. *J Biol Chem* 1999; **274**: 33179-33182 [PMID: 10559185 DOI: 10.1074/JBC.274.47.33179]

286   **Kopecki Z**, O'Neill GM, Arkell RM, Cowin AJ. Regulation of focal adhesions by flightless i involves inhibition of paxillin phosphorylation *via* a Rac1-dependent pathway. *J Invest Dermatol* 2011; **131**: 1450-1459 [PMID: 21430700 DOI: 10.1038/jid.2011.69]

287   **Mohammad I**, Arora PD, Naghibzadeh Y, Wang Y, Li J, Mascarenhas W, Janmey PA, Dawson JF, McCulloch CA. Flightless I is a focal adhesion-associated actin-capping protein that regulates cell migration. *FASEB J* 2012; **26**: 3260-3272 [PMID: 22581781 DOI: 10.1096/fj.11-202051]

288   **Jackson JE**, Kopecki Z, Adams DH, Cowin AJ. Flii neutralizing antibodies improve wound healing in porcine preclinical studies. *Wound Repair Regen* 2012; **20**: 523-536 [PMID: 22672080 DOI: 10.1111/j.1524-475X.2012.00802.x]

289   **Kopecki Z**, Ruzehaji N, Turner C, Iwata H, Ludwig RJ, Zillikens D, Murrell DF, Cowin AJ. Topically applied flightless I neutralizing antibodies improve healing of blistered skin in a murine model of epidermolysis bullosa acquisita. *J Invest Dermatol* 2013; **133**: 1008-1016 [PMID: 23223144 DOI: 10.1038/jid.2012.457]

290   **Danen EH**, Sonneveld P, Brakebusch C, Fassler R, Sonnenberg A. The fibronectin-binding integrins alpha5beta1 and alphavbeta3 differentially modulate RhoA-GTP loading, organization of cell matrix adhesions, and fibronectin fibrillogenesis. *J Cell Biol* 2002; **159**: 1071-1086 [PMID: 12486108 DOI: 10.1083/jcb.200205014]

291   **Ballestrem C**, Hinz B, Imhof BA, Wehrle-Haller B. Marching at the front and dragging behind: differential alphaVbeta3-integrin turnover regulates focal adhesion behavior. *J Cell Biol* 2001; **155**: 1319-1332 [PMID: 11756480 DOI: 10.1083/JCB.200107107]

292   **Laukaitis CM**, Webb DJ, Donais K, Horwitz AF. Differential dynamics of alpha 5 integrin, paxillin, and alpha-actinin during formation and disassembly of adhesions in migrating cells. *J Cell Biol* 2001; **153**: 1427-1440 [PMID: 11425873 DOI: 10.1083/JCB.153.7.1427]

293   **Zaidel-Bar R**, Ballestrem C, Kam Z, Geiger B. Early molecular events in the assembly of matrix adhesions at the leading edge of migrating cells. *J Cell Sci* 2003; **116**: 4605-4613 [PMID: 14576354 DOI: 10.1242/JCS.00792]

294   **Gardel ML**, Schneider IC, Aratyn-Schaus Y, Waterman CM. Mechanical integration of actin and adhesion dynamics in cell migration. *Annu Rev Cell Dev Biol* 2010; **26**: 315-333 [PMID: 19575647 DOI: 10.1146/annurev.cellbio.011209.122036]

295   **Alam A**, Neish A. Role of gut microbiota in intestinal wound healing and barrier function. *Tissue Barriers* 2018; **6**: 1539595 [PMID: 30404570 DOI: 10.1080/21688370.2018.1539595]

296   **Owen KA**, Abshire MY, Tilghman RW, Casanova JE, Bouton AH. FAK regulates intestinal epithelial cell survival and proliferation during mucosal wound healing. *PLoS One* 2011; **6**: e23123 [PMID: 21887232 DOI: 10.1371/journal.pone.0023123]

297   **Burridge K**. Focal adhesions: a personal perspective on a half century of progress. *FEBS J* 2017; **284**: 3355-3361 [PMID: 28796323 DOI: 10.1111/febs.14195]

298   **Gilmore AP**, Romer LH. Inhibition of focal adhesion kinase (FAK) signaling in focal adhesions decreases cell motility and proliferation. *Mol Biol Cell* 1996; **7**: 1209-1224 [PMID: 8856665 DOI: 10.1091/mbc.7.8.1209]

299   **Parsons JT**. Focal adhesion kinase: the first ten years. *J Cell Sci* 2003; **116**: 1409-1416 [PMID: 12640026 DOI: 10.1242/jcs.00373]

300   **Schlaepfer DD**, Mitra SK. Multiple connections link FAK to cell motility and invasion. *Curr Opin Genet Dev* 2004; **14**: 92-101 [PMID: 15108811 DOI: 10.1016/j.gde.2003.12.002]

301   **Thomas JW**, Cooley MA, Broome JM, Salgia R, Griffin JD, Lombardo CR, Schaller MD. The role of focal adhesion kinase binding in the regulation of tyrosine phosphorylation of paxillin. *J Biol Chem* 1999; **274**: 36684-36692 [PMID: 10593973 DOI: 10.1074/JBC.274.51.36684]

302   **Hu YL**, Lu S, Szeto KW, Sun J, Wang Y, Lasheras JC, Chien S. FAK and paxillin dynamics at focal adhesions in the protrusions of migrating cells. *Sci Rep* 2014; **4**: 6024 [PMID: 25113375 DOI: 10.1038/srep06024]

303   **Webb DJ**, Donais K, Whitmore LA, Thomas SM, Turner CE, Parsons JT, Horwitz AF. FAK-Src signalling through paxillin, ERK and MLCK regulates adhesion disassembly. *Nat Cell Biol* 2004; **6**: 154-161 [PMID: 14743221 DOI: 10.1038/ncb1094]

304   **Klemke RL**, Cai S, Giannini AL, Gallagher PJ, de Lanerolle P, Cheresh DA. Regulation of cell motility by mitogen-activated protein kinase. *J Cell Biol* 1997; **137**: 481-492 [PMID: 9128257 DOI: 10.1083/JCB.137.2.481]

305   **Ishibe S**, Joly D, Liu ZX, Cantley LG. Paxillin serves as an ERK-regulated scaffold for coordinating FAK and Rac activation in epithelial morphogenesis. *Mol Cell* 2004; **16**: 257-267 [PMID: 15494312 DOI: 10.1016/j.molcel.2004.10.006]

306   **Basson MD**, Sanders MA, Gomez R, Hatfield J, Vanderheide R, Thamilselvan V, Zhang J, Walsh MF. Focal adhesion kinase protein levels in gut epithelial motility. *Am J Physiol Gastrointest Liver Physiol* 2006; **291**: G491-G499 [PMID: 16899713 DOI: 10.1152/ajpgi.00292.2005]

307   **Arold ST**, Hoellerer MK, Noble ME. The structural basis of localization and signaling by the focal adhesion targeting domain. *Structure* 2002; **10**: 319-327 [PMID: 12005431 DOI: 10.1016/S0969-2126(02)00717-7]

308   **Deramaudt TB**, Dujardin D, Noulet F, Martin S, Vauchelles R, Takeda K, Rondé P. Altering FAK-paxillin interactions reduces adhesion, migration and invasion processes. *PLoS One* 2014; **9**: e92059 [PMID: 24642576 DOI: 10.1371/journal.pone.0092059]

309   **Lietha D**, Cai X, Ceccarelli DF, Li Y, Schaller MD, Eck MJ. Structural basis for the autoinhibition of focal adhesion kinase. *Cell* 2007; **129**: 1177-1187 [PMID: 17574028 DOI: 10.1016/j.cell.2007.05.041]

310   **Mousson A**, Sick E, Carl P, Dujardin D, De Mey J, Rondé P. Targeting Focal Adhesion Kinase Using Inhibitors of Protein-Protein Interactions. *Cancers (Basel)* 2018; **10** [PMID: 30134553 DOI: 10.3390/cancers10090278]

311   **Cary LA**, Chang JF, Guan JL. Stimulation of cell migration by overexpression of focal adhesion kinase and its association with Src and Fyn. *J Cell Sci* 1996; **109** (Pt 7): 1787-1794 [PMID: 8832401 DOI: 10.1242/jcs.109.7.1787]

312   **Lawson C**, Schlaepfer DD. pHocal adhesion kinase regulation is on a FERM foundation. *J Cell Biol* 2013; **202**: 833-836 [PMID: 24043698 DOI: 10.1083/jcb.201308034]

313   **Mitra SK**, Hanson DA, Schlaepfer DD. Focal adhesion kinase: in command and control of cell motility. *Nat Rev Mol Cell Biol* 2005; **6**: 56-68 [PMID: 15688067 DOI: 10.1038/nrm1549]

314   **Fan H**, Zhao X, Sun S, Luo M, Guan JL. Function of focal adhesion kinase scaffolding to mediate endophilin A2 phosphorylation promotes epithelial-mesenchymal transition and mammary cancer stem cell activities in vivo. *J Biol Chem* 2013; **288**: 3322-3333 [PMID: 23255596 DOI: 10.1074/jbc.M112.420497]

315   **McLean GW**, Carragher NO, Avizienyte E, Evans J, Brunton VG, Frame MC. The role of focal-adhesion kinase in cancer - a new therapeutic opportunity. *Nat Rev Cancer* 2005; **5**: 505-515 [PMID: 16069815 DOI: 10.1038/nrc1647]

316   **Zhao X**, Guan JL. Focal adhesion kinase and its signaling pathways in cell migration and angiogenesis. *Adv Drug Deliv Rev* 2011; **63**: 610-615 [PMID: 21118706 DOI: 10.1016/j.addr.2010.11.001]

317   **Lim ST**, Chen XL, Lim Y, Hanson DA, Vo TT, Howerton K, Larocque N, Fisher SJ, Schlaepfer DD, Ilic D. Nuclear FAK promotes cell proliferation and survival through FERM-enhanced p53 degradation. *Mol Cell* 2008; **29**: 9-22 [PMID: 18206965 DOI: 10.1016/j.molcel.2007.11.031]

318   **Teranishi S**, Kimura K, Nishida T. Role of formation of an ERK-FAK-paxillin complex in migration of human corneal epithelial cells during wound closure in vitro. *Invest Ophthalmol Vis Sci* 2009; **50**: 5646-5652 [PMID: 19494198 DOI: 10.1167/iovs.08-2534]

319   **Tanimura S**, Takeda K. ERK signalling as a regulator of cell motility. *J Biochem* 2017; **162**: 145-154 [PMID: 28903547 DOI: 10.1093/jb/mvx048]

320   **Wang Y**, Zheng J, Han Y, Zhang Y, Su L, Hu D, Fu X. JAM-A knockdown accelerates the proliferation and migration of human keratinocytes, and improves wound healing in rats *via* FAK/Erk signaling. *Cell Death Dis* 2018; **9**: 848 [PMID: 30154481 DOI: 10.1038/s41419-018-0941-y]

321   **Chodniewicz D**, Klemke RL. Regulation of integrin-mediated cellular responses through assembly of a CAS/Crk scaffold. *Biochim Biophys Acta* 2004; **1692**: 63-76 [PMID: 15246680 DOI: 10.1016/J.BBAMCR.2004.03.006]

322   **Sanders MA**, Basson MD. p130cas but not paxillin is essential for Caco-2 intestinal epithelial cell spreading and migration on collagen IV. *J Biol Chem* 2005; **280**: 23516-23522 [PMID: 15817476 DOI: 10.1074/jbc.M413165200]

323   **Sharma A**, Mayer BJ. Phosphorylation of p130Cas initiates Rac activation and membrane ruffling. *BMC Cell Biol* 2008; **9**: 50 [PMID: 18793427 DOI: 10.1186/1471-2121-9-50]

324   **Geiger B**. A role for p130Cas in mechanotransduction. *Cell* 2006; **127**: 879-881 [PMID: 17129774 DOI: 10.1016/J.CELL.2006.11.020]

325   **Cox BD**, Natarajan M, Stettner MR, Gladson CL. New concepts regarding focal adhesion kinase promotion of cell migration and proliferation. *J Cell Biochem* 2006; **99**: 35-52 [PMID: 16823799 DOI: 10.1002/JCB.20956]

326   **Raschka S**, More SK, Devadoss D, Zeng B, Kuhn LA, Basson MD. Identification of potential small-molecule protein-protein inhibitors of cancer metastasis by 3D epitope-based computational screening. *J Physiol Pharmacol* 2018; **69** [PMID: 29980145 DOI: 10.26402/jpp.2018.2.11]

327   **Wang Q**, More SK, Vomhof-DeKrey EE, Golovko MY, Basson MD. Small molecule FAK activator promotes human intestinal epithelial monolayer wound closure and mouse ulcer healing. *Sci Rep* 2019; **9**: 14669 [PMID: 31604999 DOI: 10.1038/s41598-019-51183-z]

328   **Rashmi**, More SK, Wang Q, Vomhof-DeKrey EE, Porter JE, Basson MD. ZINC40099027 activates human focal adhesion kinase by accelerating the enzymatic activity of the FAK kinase domain. *Pharmacol Res Perspect* 2021; **9**: e00737 [PMID: 33715263 DOI: 10.1002/prp2.737]

329   **Wang Q**, Gallardo-Macias R, Rashmi, Golovko MY, Elsayed AAR, More SK, Oncel S, Gurvich VJ, Basson MD. Discovery of Novel Small-Molecule FAK Activators Promoting Mucosal Healing. *ACS Med Chem Lett* 2021; **12**: 356-364 [PMID: 33738062 DOI: 10.1021/acsmedchemlett.0c00311]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com