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REVIEW

- 200** Evaluation of gastrointestinal bleeding: Update of current radiologic strategies
Parekh PJ, Buerlein RC, Shams R, Vingan H, Johnson DA
- 209** Protein kinases are potential targets to treat inflammatory bowel disease
Yang L, Yan Y

Contents

World Journal of Gastrointestinal Pharmacology and Therapeutics
Volume 5 Number 4 November 6, 2014

APPENDIX I-V Instructions to authors

ABOUT COVER Editorial Board Member of *World Journal of Gastrointestinal Pharmacology and Therapeutics*, Viviana Alicia Catania, PhD, Professor, Instituto de Fisiología Experimental-CONICET, 2000 Rosario, Argentina

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Evaluation of gastrointestinal bleeding: Update of current radiologic strategies

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Core tip: The purpose of this review will be to discuss to provide an evidence-based update on the most current diagnostic and interventional radiologic modalities available and provide clinicians with an algorithmic approach to gastrointestinal bleeding.

Parekh PJ, Buerlein RC, Shams R, Vingan H, Johnson DA. Evaluation of gastrointestinal bleeding: Update of current radiologic strategies. *World J Gastrointest Pharmacol Ther* 2014; 5(4): 200-208 Available from: URL: <http://www.wjgnet.com/2150-5349/full/v5/i4/200.htm> DOI: <http://dx.doi.org/10.4292/wjgpt.v5.i4.200>

INTRODUCTION

There are over 500000 patients hospitalized annually for gastrointestinal bleeding (GIB) in the United States, which carries an inpatient mortality rate of 3%^[1]. Patients presenting with GIB are considered as having either overt or occult GIB, depending upon the presence of visible or non-visible bleeding^[2]. Overt GIB presents as visible bleeding which constitutes melena, hematochezia or hematemesis. Occult GIB manifests as positive immunohistochemical staining or as iron deficiency anemia^[3]. Irrespectively, the initial evaluation of either overt or occult GIB includes an esophagoduodenoscopy and/or colonoscopy. Obscure GIB (OGIB) refers to the patient population with persistent or recurrent GIB where the initial endoscopic evaluation was negative, estimated to be the case in approximately 5% of patients^[3]. As a result, these patients undergo extensive testing with the objective of localizing and potentially treating the bleeding lesion. Estimates suggest that an average of \$33630 is spent per Medicare patient for further evaluation of OGIB^[4]. While radiologic advances have changed the ap-

Abstract

Gastrointestinal bleeding (GIB) is a common presentation with significant associated morbidity and mortality, the prevalence of which continues to rise with the ever-increasing aging population. Initial evaluation includes an esophagoduodenoscopy and/or colonoscopy, which may fail to reveal a source. Such cases prove to be a dilemma and require collaboration between gastroenterology and radiology in deciding the most appropriate approach. Recently, there have been a number of radiologic advances in the approach to GIB. The purpose of this review is to provide an evidence-based update on the most current radiologic modalities available and an algorithmic approach to GIB.

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Table 1 Common causes of obscure gastrointestinal bleeding based on location

Upper GI lesions	Middle GI lesions	Lower GI lesions
Cameron erosions	Less than 40 years old	Angiodysplasia
Peptic ulcer disease	Tumors	Neoplasm
Fundic varices	Meckel diverticulum	Diverticular disease
Angiodysplasia	Crohn's disease	
Dieulafoy lesion	Dieulafoy lesion	
Gastric antral vascular ectasia	Celiac disease	
	More than 40 years old	
	Angiectasia	
	NSAID enteropathy	
	Celiac disease	
	Uncommon lesions	
	Hemobilia	
	Hemosuccus pancreaticus	
	Aortoenteric fistula	

GI: Gastrointestinal; NSAID: Non-steroidal anti-inflammatory drug.

proach to GIB, the lack of an algorithmic approach and understanding of the available modalities have made it difficult for clinicians to practice cost-effective medicine. Diagnostic and therapeutic modalities differ in the setting of upper GIB (UGIB) *vs* lower GIB (LGIB). This article is intended to present the newest radiologic modalities available as it pertains to UGIB and LGIB as well as provide an algorithmic approach to GIB and the role of endoscopic markings.

ETIOLOGY

Small bowel pathology accounts for up to 75% of patients presenting with OGIB^[5-8], with angiodysplasia being the most common culprit accounting for up to 60% of these cases^[9]. Table 1 subdivides the most common causes of OGIB by anatomic location. Upper lesions are characterized by those that are proximal to the ligament of Treitz, mid lesions are distal to the ligament of Treitz extending to the terminal ileum, and lower lesions are distal to the terminal ileum^[10].

UPPER GI BLEED

Approximately 100000 are patients hospitalized annually for an UGIB, which carries a mortality rate as high as 11%^[11]. The cornerstone for diagnosis and therapeutic intervention in UGIB revolves around endoscopy. There are no radiologic approaches that have demonstrated utility in the diagnosis of an UGIB. There are, however, radiologic interventions that may be used when endoscopic therapy has proven futile, namely transjugular intrahepatic portosystemic shunt, retrograde transvenous obliteration, and transcatheter selective embolization.

Transjugular intrahepatic portosystemic shunt

Transjugular intrahepatic portosystemic shunts (TIPS) utilizes angiographic guidance to create a low-resistance communication between the hepatic vein and the intrahepatic portion of the portal vein^[12]. The expandable metal

stent maintains patency of the tract allowing for continued systemic circulation. The indication for TIPS in the setting of an UGIB include acute esophageal, gastric, or ectopic variceal hemorrhages and in the prevention of recurrent variceal bleeding.

García-Pagán *et al.*^[13] evaluated the use of TIPS in 63 patients with cirrhosis (Child-Pugh class B or C) presenting with persistent bleeding. Patients were randomly assigned to treatment with TIPS (early-TIPS; *n* = 32) or continuation of vasoactive therapy with propranolol or nadolol and long-term endoscopic band ligation (pharmacotherapy-EBL; *n* = 31) with future consideration of TIPS as rescue therapy if necessary. Re-bleeding or persistent bleeding occurred in 14 patients in the pharmacotherapy-EBL group as compared to 1 patient in the early-TIPS group during a median follow up at 16 mo (*P* = 0.001). The 1-year likelihood of remaining free from re-bleeding or persistent bleeding was 50% in the pharmacotherapy-EBL group compared 97% in the early-TIPS group (*P* < 0.001). The 1-year survival in the pharmacotherapy-EBL group compared to the early-TIPS group was 61% and 86%, respectively, which led the authors to conclude that early use of TIPS was associated with significant reduction in treatment failure and mortality in patients with cirrhosis hospitalized for acute variceal bleeding. A retrospective study in 2013 validated these results confirming a favorable 1-year mortality in patients who received early-TIPS when compared to those who received vasoactive and endoscopic therapy at 86% and 70% respectively (*P* = 0.056)^[14].

It has recently been postulated that the use of embolotherapy may further prevent recurrent variceal bleeding and stent dysfunction following TIPS creation^[15]. A recent prospective study randomized 106 patients with cirrhosis and recurrent variceal bleeding to TIPS in conjunction with prior embolotherapy *via* the jugular vein (TIPS + E, *n* = 54) or TIPS alone (*n* = 52). The 6-mo rate of shunt patency and overall rate of recurrent variceal bleeding was significantly lower in the TIPS-E cohort as compared to those patients who received TIPS alone. The 3-year cumulative rates of shunt patency, recurrent variceal bleeding and mortality were not statistically significant amongst the two groups, however, leading the authors to conclude that the TIPS-E regimen may reduce the rate of recurrent variceal bleeding during the first 6 mo but the long term benefit requires further investigation.

Retrograde transvenous obliteration

Gastric varices are an important manifestation of portal hypertension and are associated with a very high mortality rate approaching 55%^[16]. Originating from short gastric and gastroepiploic veins, cardiofundal gastric varices present with a unique vascular anatomy as they have a tendency to develop spontaneous splenorenal or gastrorenal shunts^[17]. Thus the use of cyanoacrylate *via* endoscopic sclerotherapy on gastric varices carries a risk of systemic migration through the inferior vena cava. TIPS has been performed for this reason, however is only as-

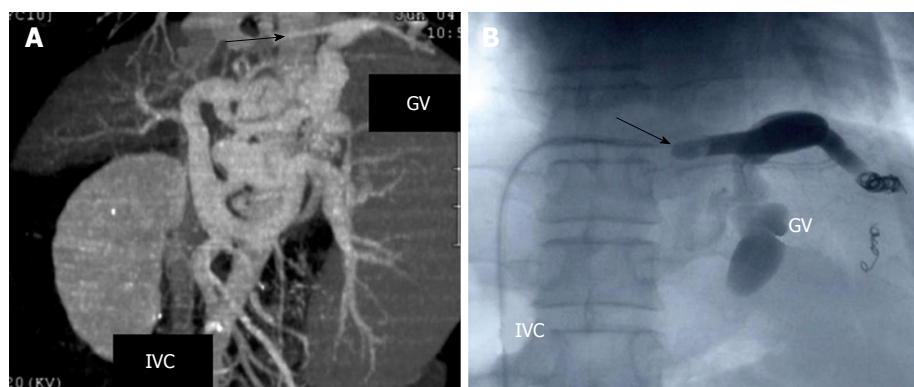


Figure 1 Balloon retrograde transvenous obliteration^[59]. A: Multidimensional computed tomography revealing varices supplied by the left gastric vein (GV) and subsequent drainage into the subphrenic vein (illustrated by the arrow) which is connected to the inferior vena cava (IVC); B: Fluoroscopic image of B-RTO depicting placement of the occlusive balloon catheter into the bleeding vessel (demonstrated by the arrow). B-RTO: Balloon-occluded retrograde transvenous obliteration.

sociated with a success rate of 50% in the regression of gastric varices and is associated with an elevated risk for the development or exacerbation of underlying hepatic encephalopathy^[18]. As a result, a new minimally invasive procedure known as retrograde transvenous obliteration (B-RTO) has been developed. This technique utilizes a sclerosing agent to thrombose gastric varices *via* a balloon catheter typically introduced through the femoral vein and left renal. Figure 1 depicts the use of B-RTO in thrombosing gastric varices.

A recent meta-analysis evaluated the outcomes for B-RTO for gastric varices^[19]. A total of 20 suitable studies were included totaling 734 patients from multiple centers. Cumulative rates for gastric variceal recurrence were reported to be 2.6% (0%-7.2%) with 1-year, 3-year, and 5-year survival rates to be 92.2% (83.1%-100%), 82.6% (71%-100%), and 67.9% (53.7%-85%), respectively. This led the authors to conclude B-RTO should be considered in the management of gastric varices when a gastorenal shunt is present. Several other retrospective studies have demonstrated technical success with B-RTO concluding it to be effective in obliterating bleeding gastric varices with good short-term outcomes^[20-22]. The use of ethanolamine oleate as a sclerosant when performing B-RTO should be with caution as recent studies have implicated it in pulmonary function disorders^[23]. The total amount of ethanolamine oleate has been shown to have a direct correlation to the extent of pulmonary damage, and thus careful respiratory monitoring may be necessary in patients undergoing B-RTO, particularly when anticipating the use of large volumes of ethanolamine oleate.

Transcatheter selective embolization

Rösch *et al*^[24] first introduced the use of transcatheter arterial embolization (TAE) in 1972 as an alternative to surgery. The advent of metallic coils, gelfoam, and surgical glue has greatly improved clinical outcomes. The procedure entails a transfemoral or brachial approach with introduction of a 5-french sheath into the common femoral artery. Subsequent arteriography is performed to delineate the anatomy and identify the culprit lesion *via* contrast

extravasation. In the event that the initial approach does not yield a culprit, then superselective catheterization of the gastroduodenal artery, left gastric artery, or splenic artery is performed depending on clinical suspicion^[25]. Once the lesions are identified then operator has a plethora of embolization techniques at his disposal, depending on the clinical scenario. The choice of the best embolic agent, however, remains an area of debate. Figure 2 depicts the use of TAE in a gastrointestinal (GI) bleed.

Recently, there have been several retrospective analyses comparing the efficacy of TAE to surgery as salvage therapy following failed endoscopic therapy in the setting of UGIB^[26,27]. These studies found TAE to be efficacious in controlling life threatening bleeds from an UGI source in high-risk patients who would otherwise be subjected to emergency surgery, which carries a substantially higher mortality rate (nearly 5 times) when compared directly to TAE.

Intra-arterial vasopressin infusion

Vasopressin elicits contractions of smooth muscles in mesenteric vasculature, thus decreasing perfusion pressure to the bowel and potentially thrombosing the bleeding site^[28]. Vasopressin is directly infused into the suspected artery at a rate of 0.2-0.4 U/min until control of bleeding is observed on angiography. Once control is documented, vasopressin is infused into the mesenteric artery for another 12-48 h depending on severity.

A review of the literature demonstrated an initial success rate of 70%-80% with use of intra-arterial vasopressin infusion^[28]. Unfortunately, the rate of re-hemorrhage with refractory bleeding ranged from 20%-40%. There were various theories that emerged regarding vasopressin failure, namely the rich collateral supply to the upper GI tract, however the exact reason remains unproven. At present time, the emergence of embolotherapy has put vasopressin infusion out of favor.

The bottom line

Endoscopy is the point of focus in identifying the culprit of an UGIB and in delivering initial treatment. There are

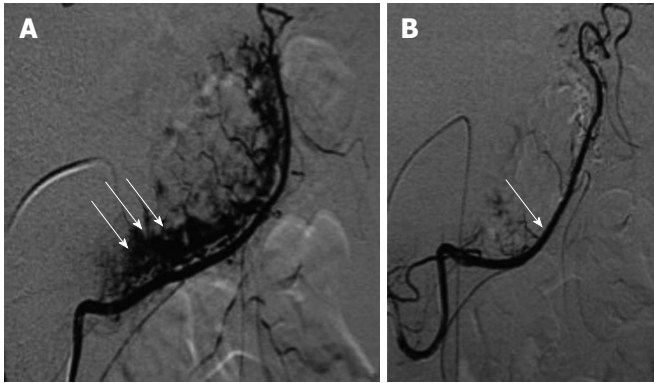


Figure 2 Selective transarterial embolization^[60]. A: Selective catheterization of the right gastro epiploic artery in the setting of angiodysplasia. The arrows depict the pathologic vessels at the greater curvature of the stomach; B: Post embolization angiogram revealing control of the bleeding vessel.

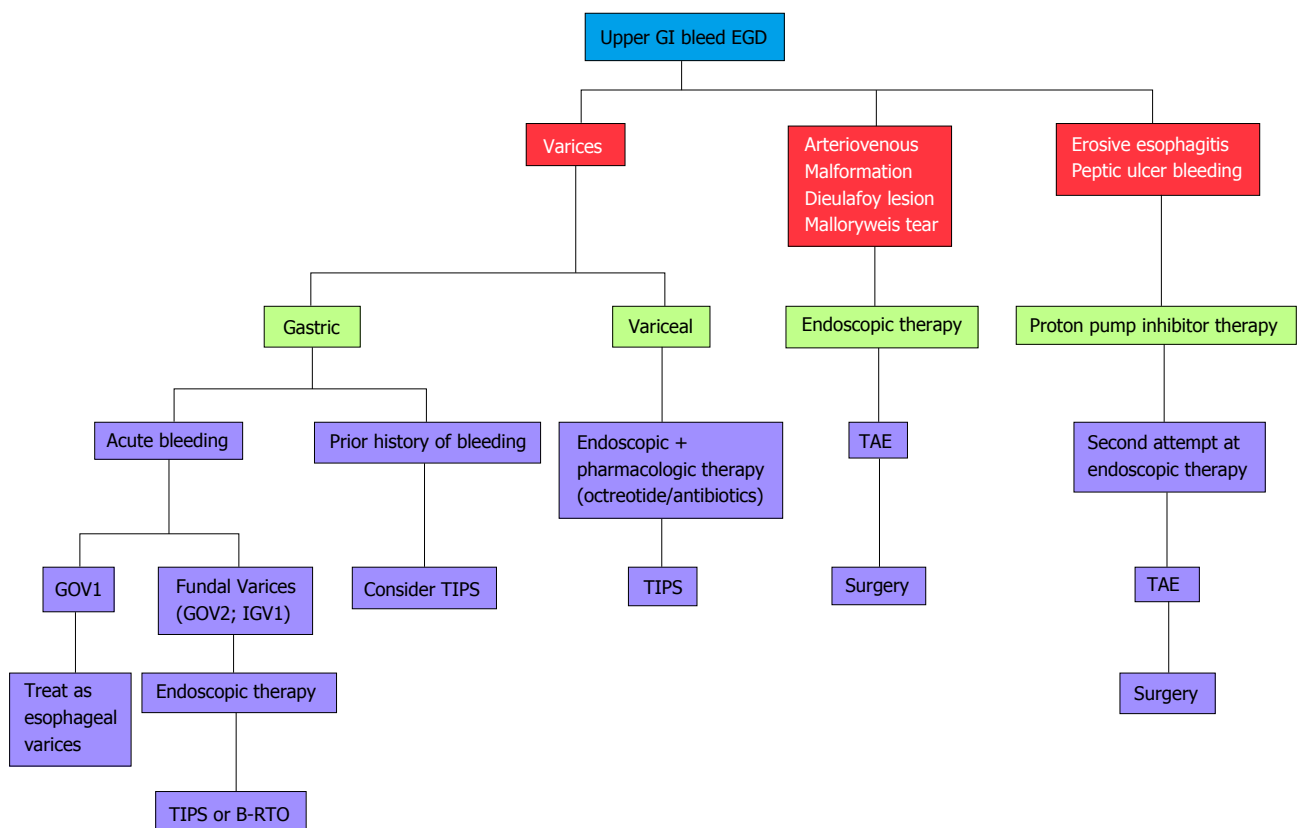


Figure 3 Algorithmic approach to upper gastrointestinal bleeding. EGD: Esophagoduodenoscopy; TAE: Transcatheter arterial embolization; TIPS: Transjugular intrahepatic portosystemic shunt; GOV1: Gastroesophageal Varices 1; B-RTO: Balloon-occluded retrograde transvenous obliteration; GI: Gastrointestinal; IGV: Isolated gastric varices.

no radiologic modalities that have been proven to show diagnostic utility in the setting of UGIB. When endoscopy proves unsuccessful, however, there are several radiologic alternatives that can potentially treat the underlying lesion including TIPS, B-RTO, and TAE. Figure 3 provides an algorithmic approach to a patient with UGIB.

LOWER GI BLEED

The incidence of LGIB is approximately 20 per 100000 persons^[29] with an associated all cause mortality of 3.9%^[30].

In addition, patients who experience LGIB during a hospitalization for another condition seem to have a higher mortality when compared to those who are admitted with LGIB as their chief complaint^[31]. The differential diagnosis of LGIB ought to include UGIB being that 10%-15% of patients with severe hematochezia are found to have an upper GI source^[32]. Hemorrhoidal bleeding is the most common cause of LGIB followed by diverticular bleeding, and next by vascular ectasia^[33]. This section will dissect the various tools available for approaching a patient with a LGIB.

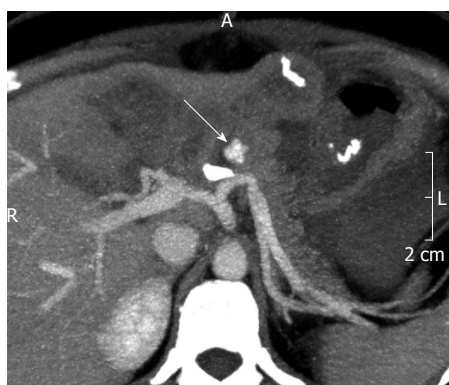


Figure 4 Unenhanced computed tomography showing contrast media extravasation anterior to the splenic artery^[61].

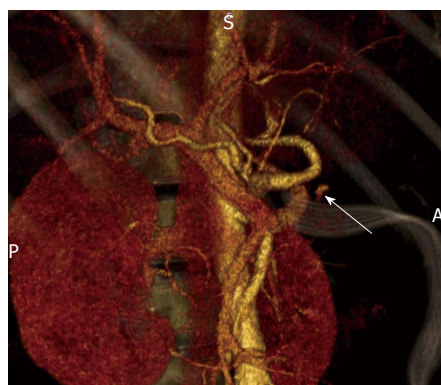


Figure 5 Multiphasic multidetector computed tomography angiography (arterial phase) showing extravasation anterior to the splenic artery^[61].

Technetium-labeled red blood cell bleeding scan

Technetium-labeled red blood cell bleeding scan (RBC scan), or scintigraphy, is typically the first approach utilized in the localization of an active LGIB. Red blood cells tagged with technetium (99 mTc) are re-injected into the patient with sequential monitoring for extravascular activity. Frequently, images are obtained over 30 to 90 min, and then, if necessary, every few hours for up to 24 h.

Brunnler *et al.*^[34] performed a retrospective analysis of 92 patients evaluating the role of technetium-labeled red cell bleeding scan in patients with OGIB. Scintigraphy was able to demonstrate a positive result in all cases, with a false positive rate of only 4%. Notably, a heparin provocation test (a diagnostic approach to localizing the lesion in OGIB which will be later discussed in further detail) increased the diagnostic yield by 46% in patients with a primary negative scan. Scintigraphy (\pm heparin provocation) is a reliable modality in localizing the lesion in approximately half of OGIB cases.

Advantages and disadvantages

There are two major advantages to the use of scintigraphy. The first is that scintigraphy only requires an active bleeding rate of 0.1 to 0.4 mL/min making it the most sensitive modality in detecting an active GIB^[35,36]. The second benefit is the immediate ability to test patients without any need for preparation prior to the procedure.

There are two major disadvantages to the use of scintigraphy. First, it does not offer any therapeutic capabilities, therefore in the setting of a positive scan a second procedure, *i.e.*, endoscopy, catheter directed angiography or surgery must subsequently be performed^[37]. A second major detriment to the use of scintigraphy is that it can only localize an active bleed to a general area and not a specific location. This occurs as blood moves secondary to peristaltic or anti-peristaltic actions. As a result, accuracy rates in the literature have varied ranging from 24%-91%^[38-40]. Hunter *et al.*^[41] demonstrated these difficulties by evaluating the outcome of 203 patients who underwent scintigraphy for LGIB. Scintigraphy was positive in 52 patients (26%), who subsequently underwent further evaluation. A definitive bleeding site was identified in

22 patients with only 8 cases correlating to scintigraphy.

Multiphasic multidetector computed tomography angiography

Until recently, computed tomography only played a minor role in the evaluation of GIB. The introduction of multiphasic multidetector computed tomography angiography (MDCTA) transformed this modality into an important tool in detecting, localizing, and characterizing active GIB. Most institutions utilize MDCTA with a 64-detector-row scanner in three phases: unenhanced, arterial, and portal-venous^[42]. Comparing the arterial and portal-venous phase images to the unenhanced images is critically important in avoiding false-positive results. Active GIB often appears as extravasated contrast material in the bowel lumen or bowel wall during the arterial phase and increases throughout the portal-venous phase (> 90 HU, but typically ranging from 115-300 HU)^[42-45]. Figures 4 and 5 depict the various phases of MDCTA in the setting of an active arterial bleed anterior to the splenic artery.

Wu *et al.*^[46] performed a meta-analysis evaluating the accuracy of CTA in the diagnosis of acute GIB, which included a total of 9 studies with 198 patients in total. The pooled results showed a sensitivity of 89% and specificity of 85% proving MDCTA to be an accurate tool in the setting of an acute GIB. Recently published were the results of a 5-year prospective trial evaluating the utility of MDCTA in active GIB^[47]. There were a total of 113 patients enrolled with clinical signs of active GIB who underwent MDCTA. The investigators found the overall sensitivity, specificity, positive and negative predictive values of MDCTA to be 86%, 100%, 100%, 61% and 89%, respectively, concluding that MDCTA is an accurate first line screening method for detection and localization of GIB.

Advantages and disadvantages

Angiography requires active blood loss of at least 0.5 mL/min^[48] in order to visualize the bleeding vessel. The major advantage of MDCTA over other modalities is that it does not require any preparation and yet localization is accurate.

A major disadvantage to the use of MDCTA is the substantial radiation exposure the patient incurs. Other serious complications include cardiac arrhythmias, bowel ischemia, and a rebleeding rate in as high as 50% of patients^[49]. Lastly, the use of contrast media often times precludes patients with renal failure. As always, the risk benefit ratio must be taken into account of worsening renal insufficiency *vs* on-going GIB. The literature varies in defining a creatinine clearance (CrCl) (most institution use a threshold value for creatinine of 1.7 and CrCl of 45 mL/min) precluding patients from MDCTA, however pre-procedural hydration and administration of n-acetylcysteine has been proven to prevent contrast induced nephropathy and worsening renal function in high-risk patients^[50]. It should be noted that there are no contraindications to the use of intravenous contrast for end-stage renal patients on chronic hemodialysis.

Computed tomography enterography and magnetic resonance enterography

Computed tomography enterography (CTE) and magnetic resonance enterography (MRE) are non-invasive alternatives used to determine the etiology of OGIB, particularly small bowel pathology^[51]. Huprich *et al*^[52] evaluated the findings of CTE in 22 outpatients with OGIB^[53]. This retrospective study compared findings on CTE with capsule and traditional endoscopic, surgical, and angiographic findings. CTE findings were positive for a bleeding source in 45% of patients, with 80% of findings also positive with subsequent capsule endoscopy or clinical diagnosis. In addition, CTE correctly identified 3 lesions undetected by capsule endoscopy. A recent prospective study evaluated the use of CTE in 35 patients with OGIB, both overt ($n = 20$) and occult ($n = 15$)^[54]. They found positive findings in 46.9% of CTE scans and as a result 12 patients underwent subsequent laparotomy. The surgical findings in all 12 cases were in conformity with the findings on CTE leading the authors to conclude CTE to be a useful diagnostic tool in the evaluation of both overt and occult OGIB. Since MRE is relatively new to clinical practice, there is limited data available for its use in GIB and thus may be an area of further research in the future.

Advantages and disadvantages

There are several advantages to the use of CTE and MRE, namely the ability to visualize the thickness of the bowel wall in its entirety and provide a global overview of visceral structures within the abdomen^[54]. This allows for not only diagnosis but also staging of small bowel pathology.

The major disadvantage of CTE, but not MRE, is the radiation exposure to the patient^[48].

Another detriment to the use of both CTE and MRE is that they do not have the necessary capabilities to perform therapeutic maneuvers. In addition, pre-existing high attenuation material within the bowel may decrease the diagnostic yield of CTE. Lastly, patients with on

chronic hemodialysis should be precluded from receiving gadolinium due to risk of nephrogenic systemic fibrosis.

Provocative angiography

Provocative angiography is a salvage method used to localize the source of bleeding in patients with OGIB when all other radiologic and endoscopic approaches have been exhausted^[55]. The technique involves the addition of anticoagulants, vasodilators and fibrinolytics during angiography to induce a hemorrhagic state with intent to localize the bleeding vessel.

The use of provocative angiography remains controversial due to theoretical increased risk of exacerbating the bleed. A recent prospective analysis evaluated the diagnostic yield and complication rate in 36 patients with LGIB who underwent provocative angiography^[56]. Each patient was subjected to heparin followed by selective transcatheter injection of a vasodilator and plasminogen activator into the vessel of high suspicion. They found that 31% of angiograms resulted in visible extravasation and the identification of a source of LGIB in 33% of cases overall. A total of 31% underwent successful definitive treatment of LGIB with only one embolization-related complication requiring surgical resection. This led the authors to conclude provocative angiography to be a safe and effective means for eliciting the source of occult LGIB leading to a definitive therapy in up to 33% of patients.

The bottom line

Colonoscopy remains the mainstay to diagnose the etiology of LGIB in most patients who are hemodynamically stable. In a hemodynamically unstable patient with active bleeding, scintigraphy and MDCTA are two radiologic approaches that can be utilized to identify the source. In a patient with intermittent GIB or OGIB, scintigraphy and MDCTA may prove futile. In this case, capsule endoscopy, single-balloon/double-balloon/spiral enteroscopy, and CTE are modalities used to identify and potentially treat the underlying lesion. Provocative angiography is a last resort tool when all other endoscopic and radiologic alternatives have been exhausted. There is relatively limited data on the use of MRE in OGIB, and thus may be an area requiring further research. Figure 6 provides an algorithmic approach to a patient with LGIB.

THE ROLE OF ENDOSCOPIC MARKINGS

Gastroenterologists may facilitate interventional radiologic procedures through the placement of endoscopic markings typically involving a MRI compatible metallic clip. Eriksson *et al*^[57] recently evaluated the utility of endoscopic marking with a metallic clip in TAE for patients with UGIB. They placed a metallic clip in the fibrous edge of the ulcer adjacent to the bleeding point in 13 patients. In 10 patients, subsequent TAE was indicated due to persistent or recurrent bleeding. The artery was embolized with microcoils in close proximity to the clip. Of

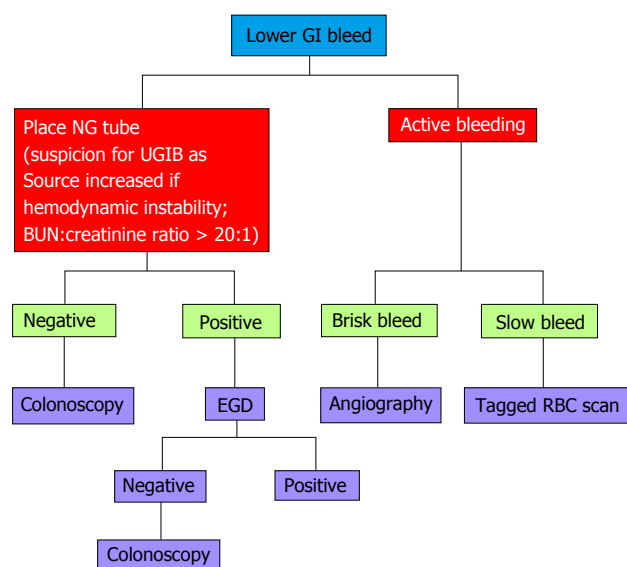


Figure 6 Algorithmic approach to lower gastrointestinal bleeding. EGD: Esophagoduodenoscopy; GI: Gastrointestinal; NG: Nasogastric; BUN: Blood urea nitrogen; RBC: Red blood cell; UGIB: Upper gastrointestinal bleeding.

the 10 patients, hemostasis was achieved in 8 patients and in 6 the clip was essential in identifying the bleeding vessel. Another recent prospective study evaluated the utility of rotational angiography after endoscopic marking in patients with acute bleeding ulcers with similar results^[58].

The bottom line

Endoscopic markings facilitate interventional radiologic procedure by helping to accurately localize the bleeding focus thus enhancing the possibility that the correct vessel is embolized. This can minimize the risk of recurrent bleeding after embolization and preclude further unnecessary procedures.

CONCLUSION

Recently, there have been many radiologic advances in the diagnostic and therapeutic approach to GIB. In order to optimize patient care and practice cost effective medicine, it is essential for the clinician to familiarize themselves with advantages and limitations of these new modalities. Since the approach to UGIB differs greatly from LGIB, it is necessary to have an algorithmic approach to a patient presenting with each such as those we have suggested. The recommendations and the strengths and weaknesses of the modalities discussed in this review are based on the best evidence available at this time.

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Protein kinases are potential targets to treat inflammatory bowel disease

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Abstract

Protein kinases play a crucial role in the pathogenesis of inflammatory bowel disease (IBD), the two main forms of which are ulcerative colitis and Crohn's disease. In this article, we will review the mechanisms of involvement of protein kinases in the pathogenesis of and intervention against IBD, in terms of their effects on genetics, microbiota, mucous layer and tight junction, and the potential of protein kinases as therapeutic targets against IBD.

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Key words: Inflammatory bowel disease; Protein kinase; Barrier function; Microbiota; Genetics

Core tip: The roles of protein kinases in the pathogenesis and intervention of inflammatory bowel diseases (IBD) are emerging. In this article, we will review the specific roles of different protein kinases in the pathogenesis of IBD, classify these protein kinases into different categories based on their fundamental functions in IBD, and describe substantial new mechanistic insights into the pathogenesis of IBD, highlighting protein kinases as potential intervention targets against IBD.

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INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD), two main forms of inflammatory bowel disease (IBD), are relapsing, idiopathic intestinal inflammatory conditions, caused by inappropriate and continuing immunologic responses to aberrant intestinal microorganisms in genetically susceptible individuals under certain environmental conditions^[1].

UC and CD differ^[2] with each other dramatically in different respects. UC is confined to the superficial area of the intestinal wall, whereas CD is transmurally distributed throughout the entire digestive tract but in a discontinuous way. The lesion is patchy with "lead pipe sign" in UC, but many polyps with "string sign" are often observed in CD. UC displays a Th2-like immune response, while CD shows a Th1 dominant response. Antineutrophil cytoplasmic antibodies were found in 65% of UC cases and 5%-10% of CD cases, and antibodies to yeast *S. cerevisiae* were found in 60%-70% of CD cases and 10%-15% of UC cases^[3]. Meanwhile, UC and CD share many similarities, such as neutrophil infiltration and epithelial barrier dysfunction. Despite the fact that there is no cure for IBD thus far, enormous progress about the pathogenic mechanisms of this inflammatory disorder has been around the corner in different aspects, such as genetics, regulatory immunology and microbiome.

The signaling pathways mediated by protein kinases have drawn much attention for connecting external stimuli including hostile environmental stresses with internal biological responses, such as intestinal inflammation. Protein kinases can be defined as enzymes which add phosphate

Table 1 Protein kinases related to inflammatory bowel disease genetics

Kinase	IBD	Ref.
ERK1	CD	[8]
p38	CD and UC	[9]
TYK2	CD and UC	[10]
JAK2	CD and UC	[11]
GCKR	CD	[12]
CDKAL1	CD	[13]
LRRK2	CD	[15]

ERK1: Extracellular signal-regulated Kinase; TYK2: Tyrosine kinase 2; JAK2: Janus kinase 2; GCKR: Glucokinase regulator; CDKAL1: Cyclin-dependent kinase 5 regulatory subunit-associated protein 1-like; LRRK2: Leucine-rich repeat kinase 2; IBD: Inflammatory bowel diseases; UC: Ulcerative colitis; CD: Crohn's disease.

(called phosphorylation) to the side chain of serine, threonine or tyrosine of substrate molecules. This modification alters the biological function of the substrate, such as changing enzyme activity, cellular distribution, and even causing diseases^[4,5]. In this review, we will shed light on the roles of protein kinases in the pathogenesis of intestinal inflammation and describe some new mechanistic insights into the intervention of IBD, which targets at protein kinases.

PROTEIN KINASES AND GENETIC FACTORS

Genome-wide association studies demonstrated that genetic factors are very crucial in the individual susceptibility to IBD, for example, relatives of UC patients including twins display almost ten times greater risk of UC than non-relatives^[6,7]. As shown in Table 1, major IBD susceptibility regions on chromosomes 16 and 6 contain some genes encoding protein kinases like extracellular signals-regulated kinase 1 (ERK1)^[8] and p38^[9]. Several single-nucleotide polymorphisms in tyrosine kinase 2^[10] and Janus kinase 2^[11] were identified in IBD patients. Glucokinase regulator has also been associated with the risk of CD^[12]. The cyclin-dependent kinase 5 regulatory subunit-associated protein 1-like plays an important role in susceptibility to CD, psoriasis and type II diabetes^[13,14]; leucine-rich repeat kinase 2 is identified to be related to the pathogenesis of CD^[15].

PROTEIN KINASES AND MICROBIOTA

Up to 10^{14} individual bacteria in the human gastrointestinal (GI) tract^[16], together with the mucous layer where the microbiome lives in, constitute the first line of defense in host against hostile external environment, modulating GI tract development, maintaining immune homeostasis, and regulating host metabolism rate. The bacterial abnormality plays a dominant role in the onset and development of IBD.

Commensal bacteria and host innate immune system

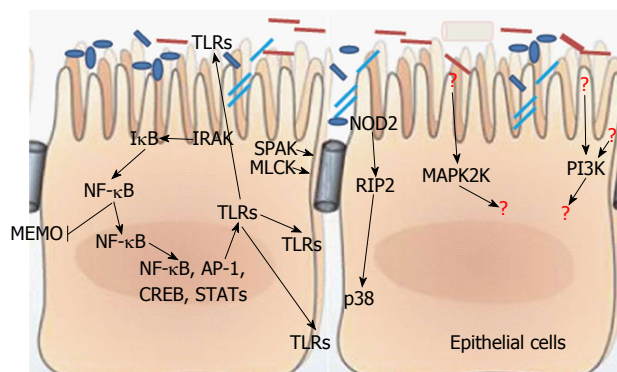


Figure 1 Intestinal epithelial cells use a variety of different molecules including protein kinases to monitor the presence of microbial pathogens, commensal bacteria, or host-generated products. Pathogen-recognition receptors, including TLRs, NOD2, and NLRs, are located on and within the cell where they recognize different threats. Recognition results in NF-κB activation, leading to the production of cytoprotective factors when stimulated by commensal bacteria and proinflammatory products when stimulated by potential pathogens, or blocks the activity of NEMO. Some other undefined factors can stimulate protein kinases such as PI3K or MAPK2K to regulate the process of intestinal inflammation. TLR: Toll like receptor; IRAK: Interleukin 1 receptor associated kinase; IκB: Inhibitor kappa B; NF-κB: Nuclear factor kappa B; SPAK: Ste20 like proline/alanine rich kinase; NEMO: NF-kappa-B essential modulator; MLCK: Myosin light chain kinase; CREB: cAMP response element binding protein; STAT: Signal transducer and activator of transcription; NOD2: Nucleotide-binding oligomerization domain-containing protein 2; NLRs: NOD-like receptors; RIP2: Receptor-interacting protein kinase 2; PI3K: Phosphoinositide 3 kinase; MAPK2K: Mitogen-activated protein kinases 2 kinase; AP-1: Activator protein 1.

evolve together and thus maintain mucosal immune homeostasis by balancing inflammatory responses and regulating a variety of bacteria-triggering signal transduction pathways^[17], such as uncoupling nuclear factor (NF)-κB or mitogen activated protein kinase (MAPK) dependent target genes in a negative feedback manner^[18,19]. The host's innate immune system is poised to be triggered by signs of bacterial challenge, specially, some pathogen-associated molecules such as flagellin, peptidoglycan, lipoteichoic acid, or lipopolysaccharide, together called pathogen-associated molecular patterns which can wake up the host innate immune system^[20,21] and be further sensed by pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) or the nucleotide-binding oligomerization domain containing protein (NOD)-like receptors^[22] (Figure 1). These PRRs would then induce the activation of signaling cascades, mostly MAPK and NF-κB pathways. In terms of MAPK pathways, it follows MAP4K-MAP3K-MAP2K-MAPK pattern, and then, the activated MAPK undergoes translocation to the nucleus to activate molecules required for gene transcription, including inflammatory molecules^[23,24]. For example, anthrax toxin can induce macrophage death by inhibiting the p38 signaling pathway^[25,26], and MAPK-activated protein kinase 2 plays an important role in the pathogenesis of *Clostridium difficile*-associated intestinal inflammation^[27]. For the NF-κB pathway, after being activated by IκB kinase complex, it phosphorylates α subunit of IκB, the inhibitor of NF-κB. Phosphorylation of IκB, accompanied by its ubiquitination and proteolytic degrada-

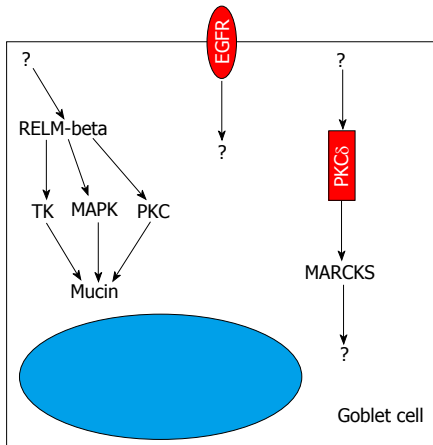


Figure 2 Intestinal Goblet cells employ different mechanisms including protein kinase related pathways to modulate the secretion of mucus, such as pathways related to tyrosine kinase, protein kinase C delta, myristoylated alanine-rich C-kinase substrate or receptors with tyrosine kinase activity such as epidermal growth factor receptor. MARCKS: Myristoylated alanine-rich C-kinase substrate; EGFR: Epidermal growth factor receptor; TK: tyrosine kinase; RELM-beta: Resistin-like molecule beta; PKCδ: Protein kinase C delta; MAPK: Mitogen activated protein kinase.

tion, results in exposure of the nuclear localization signal (NLS) on the now unbound NF- κ B^[28], which will further facilitate nuclear translocation of NF- κ B and be followed by transcriptional activation of many genes. In addition, even being regarded as an molecule which can promote inflammatory responses, an anti-inflammatory effect of NF- κ B was noticed; absence of NF- κ B essential modulator kinase causes spontaneous severe colitis, but commensal bacteria can stimulate the NF- κ B pathway to protect the host from exacerbating consequence^[29]. Blockage of epithelial NF- κ B pathway will deteriorate this colitis by increasing the translocation of bacterial to the mucosa^[30]. Besides the MAPK and NF- κ B pathways, some other signaling pathways are also very important, for example, after recognition of *Salmonella* enterica serovar *Typhimurium* curli fibrils in the gut, the TLR2-phosphatidylinositol 3 (PI3)-kinase pathway will be stimulated to tight the epithelial barrier^[31]. However, PI3 kinase signaling promotes *Campylobacter jejuni*-induced colitis through neutrophil recruitment in mice^[32]. RIP2 tyrosine kinase activity is required for NOD2-dependent autophagy process, but plays a dual role in this process. RIP2 sends a positive autophagy signal through activation of p38 MAPK and further relieves repression of autophagy mediated by the phosphatase PP2A^[33]. Not like NOD2 whose signaling induces cryptidins, MyD88-mediated TLR signaling induces RegIIIg and α -defensins, and more importantly, regulates bacterial infection-related mucosal immunity^[34-36]. In parallel, protein kinase C (PKC) can mediate the function of MyD88 adaptor-like (Mal) molecule in the maintenance of epithelial barrier integrity^[37].

PROTEIN KINASES AND BARRIER DYSFUNCTION

Basically, IBD is characterized by passive leaky diarrhea

and compromised intestinal barrier function. Except for the fact that commensal bacteria function as primary line of defense, protein kinases are also important in regulating the intestinal barrier function.

Mucus layer

The luminal side of the intestine is covered by a mucus layer which provides protection to the mucosa from mechanical damage and invasion of pathogens, and, together with commensal bacteria, constitutes a physical barrier between the epithelium and luminal contents including pathogenic bacteria, viruses, and parasites^[38,39]. This gel-like mucus layer can be divided by two distinguished layers-the outer and inner layers. The vast majority of intestinal bacteria, viruses and even parasites live in the flowing outer mucus layer; the inner layer is, however, an unstirred and relatively sterile layer adjacent to epithelial surface. The sterility of the inner layer accredits to the preservation of huge amounts of defensins, cathelicidins, and cryptidins with important function of anti-intestinal pathogens. Mucin coding gene *muc2*^{-/-} mice demonstrated spontaneous colitis because of increased transepithelial permeability^[40], in which bacteria can stick to the surface of the intestinal mucosa, which facilitates the translocation of bacteria into lower crypts and epithelial cells, thus triggering an inflammatory response^[39,41]. Protein kinases are involved in the integrity and maintenance of these mucus layers (Figure 2). Epidermal growth factor receptor (EGFR), harboring tyrosine kinase (TK) activity, has critical functions in development, growth, differentiation, proliferation and repair of epithelial cells^[42,43]. After stimulation by EGFR ligands such as transforming growth factor- α and epidermal growth factor, epithelial cells can develop into a mucous phenotype^[44,45]. However, inhibition of EGFR tyrosine kinase activity can abolish the effects of EGFR ligands on mucus production both *in vivo* and *in vitro*. PKC δ stimulates the secretion of mucin in the epithelium *via* regulation of myristoylated alanine-rich protein kinase C substrate pathway^[46]. Treatment of epithelial cells with PD98059 (MEK inhibitor) can inhibit MAPK activity and block the expression of terminal differentiation markers, such as sucrase-isomaltase, ITF, and MUC2, thereby interfering with the production of mucin^[47]. Some kinases like ERKs, TK, and PKC^[48] can regulate the production of mucin by mediating the activity of resistin and resistin-like molecule-beta; cathelicidin up-regulates MUC1 and MUC2 expression through MAPK pathway to modulate mucus synthesis^[49].

Protein kinase and epithelial junctions

The intestinal monolayer is characterized by polarization of apical and basolateral sides. The apical membrane is generally impermeable to hydrophilic solutes and contributes predominantly to mucosal barrier^[41]. Among the most important structures to determine paracellular permeability of the intestinal barrier are the epithelial tight junctions (TJs), which are made up of multiple proteins such as occludin and claudins^[50]. Occludin as the first

identified TJ^[51], plays an important role in epithelial/endothelial barrier integrity, and disruption of occludin regulation is an important aspect of a number of diseases^[52-54]. The claudins, as a group of TJ proteins with approximately 24 members, interact with numbers of other cell structures and affects junctional function^[55-58]. Claudins are expressed in a tissue-specific manner and may show distinct functions, for example, in the colon are expressed the claudins-1, 2, 3, 4, 5, 7, and 8; the claudin-2 is a pore-forming TJ protein, but claudins-1 and 4 are barrier tightening proteins^[59-63]. 12-O-tetradecanoylphorbol-13-acetate can increase transepithelial electrical resistance by activating different isoforms of PKC and enhancing the expression of TJ proteins ZO-1, 2, occludin and claudin-1^[64,65]. Ca²⁺/calmodulin-dependent protein kinase II can compromise endothelial barrier function^[66]. Ras-transfected epithelial cells demonstrated compromised barrier function; however, inhibition of the MAPK signaling pathway can restore the morphology of epithelial cells and the TJ assembly. Further, the phosphorylation of tyrosine residues in occludin and ZO-1 may be crucial for the formation of TJ^[67]. cAMP-dependent protein kinases regulate epithelial barrier function by phosphorylation of claudin-3^[68,69].

Generally, at least two relatively independently routes known thus far are responsible for communication between host and external environment through paracellular pathway, both of which can be regulated by protein kinases^[70-72]. The size-selectivity related paracellular pathway is one of the two routes, which facilitates transepithelial passage of different size of molecules, such as lipopolysaccharides^[71,72], and can be regulated by protein kinases, such as MAPKs, Ste20 like proline/alanine rich kinase (SPAK)^[73], PKC^[64,65] and myosin light chain kinase (MLCK)^[74]. Another route, also called charge-selectivity route, is composed of pore-forming proteins claudins^[75-77]. Dysfunction of these two routes, either size-dependent or charge-dependent pathway, may result in the abnormality of overall epithelial TJ, which provides an even more leaky gut. This situation will facilitate the contact of intestinal microorganisms including bacteria, viruses and parasites with the host's immune system, resulting in altered production of inflammatory mediators that contribute to the compromised barrier function.

Mucosal permeability is influenced by many different factors in there distinct ways. Except the mucus layer, microbiota and epithelial cells themselves mentioned above, genetic factors play crucial roles in the regulation of intestinal barrier function^[6]; innate and adaptive immune systems can interfere with epithelial permeability in a dramatic manner^[78]; autonomic nerves, like enteric glial nerve ablation, can perish epithelial permeability to develop fulminant jejunoileitis^[79]. However, barrier dysfunction itself, like in MLCK^[74] and SPAK^[73] gene modified mice, does not necessarily mean that the mice are destined to develop intestinal inflammation, implying formidable compensation in host.

PROTEIN KINASES AND PATHOGENESIS OF IBD

MAPKs

Notably, protein kinases play very crucial roles in many aspects of pathogenesis of IBD, highlighting their emerging roles as potential therapeutic targets against IBD. Besides the NF- κ B pathway, the MAPK signaling pathway is another highlighted pathway involved in many different diseases including IBD^[80]. The activation of MAPK-ERK1/2 phosphorylates the downstream proinflammatory proteins such as cytosolic phospholipase A2 and some transcription factors such as activated proteins, Ets-1, Elk and c-myc. Interestingly, ERK1/2, by a study using an ERK1/2 inhibitor, was found to play an important role in the function of immune cells and other cell types during IBD, by regulating some pro-inflammatory mediators [such as interleukin-1 (IL-1)] related signaling transduction^[81,82], evidenced by their enhanced expression and phosphorylation status during IBD^[83,84]. Furthermore, the "tightening" junction protein claudin-4, which plays an important role in epithelial barrier function, is regulated by protein kinase ERK^[85]. By inducing Akt but blocking p38 signaling, *Lactobacillus* GG prevents cytokine-induced apoptosis of intestinal epithelial cells, indicating p38 and Akt as key mediators of epithelial barrier function^[86,87]. p38 activity is increased significantly in tissues from IBD patients and in mouse models of colitis^[83,84,88], in which inhibition of p38 lowers KC (IL-8) and IL-6 production. A similar result was reported that *heat-killed Lactobacillus brevis* phosphorylates p38 kinase to regulate the expression of proinflammatory cytokines such as TNF- α , and to improve intestinal integrity^[89]. JNK1/2 kinase activity was enhanced in IBD inflamed tissue and blockage of JNK1/2 in experimental colitis reduced the production of proinflammatory cytokines^[84,90,91].

Serine and threonine kinases

SPAK: SPAK is a serine/threonine kinase containing an N-terminal series of proline and alanine repeats (PAPA box) followed by a kinase domain, an NLS, a consensus caspase cleavage motif, and a C-terminal regulatory region^[92]. Colonic SPAK presents as a unique isoform that lacks the PAPA box and F-helix loop in the N-terminus^[93]. The diversity of domains in SPAK might be associated with a variety of biological roles. For example, SPAK was reported to play roles in cell differentiation, transformation and proliferation, and regulation of chloride transport^[94,95]. More importantly, a linkage has been established between SPAK and inflammation. SPAK as an upstream kinase to Na⁺-K⁺-2Cl-co-transporter 1 (NKCC1), can phosphorylate NKCC1 and play an important role in inflammation^[96]. Further, we have demonstrated that SPAK can activate the p38 pathway^[93]. Decreased expression of SPAK contributes to enhanced intestinal barrier, and thus SPAK knockout mice were more tolerant to experimental colitis induced by dextran sodium sulphate (DSS) with

decreased intestinal microorganism translocation into the mucosa and inhibition of the production of inflammatory mediators^[97].

MLCK: MLCK is named after its phosphorylation of MLC to induce contraction of the perijunctional actomyosin ring, and it is indispensable for tumor necrosis factor (TNF) related barrier dysfunction. In turn, TNF can induce the phosphorylation and transcription of MLCK^[98,99]. Constitutive MLCK activation in the intestinal epithelium increases intestinal paracellular permeability and aggravates the severity of colitis in mouse models. However, blockage of MLCK activation can increase significantly the intestinal barrier function and ameliorate DSS-induced colitis^[100].

PKC: PKC has a variety of isoforms that are involved in the pathogenesis of IBD by their effect on the mucus layer^[101], microbiota^[34-37], cell junction^[64,65] and immune system. Specially, PKC θ plays an important role in T cell receptor activation and signaling^[102], and PKC δ is crucial for B cell tolerance^[103,104]. PKC η can control CTLA-4-mediated regulatory T cell (Treg) function^[105]; however, PKC- θ inhibits Treg function, implying its blocking of Treg-mediated suppression. Inhibition of PKC- θ stimulates Treg, resumes compromised Treg function in rheumatoid arthritis patients, and enhances protection against experimental colitis in mice. As a result, PKC- θ mediates negative feedback on Treg cell function^[106].

CONCLUSION

Protein kinases and the related signaling transduction pathways are involved in many physiological and pathological processes such as development, inflammation (for example, intestinal inflammation) and tumorigenesis. In this review, we shed some light on the roles of protein kinases in terms of their effect on IBD-related genetic factors, microbiota, mucus layer, epithelial cell and the tight junction. Further studies are needed to explore the feasibility and application of these signaling pathways in the control of IBD.

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Organization as author

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Statistical data

Write as mean \pm SD or mean \pm SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as *v* (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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Use SI units. For example: body mass, *m* (B) = 78 kg; blood pressure, *p* (B) = 16.2/12.3 kPa; incubation time, *t* (incubation) = 96 h; blood glucose concentration, *c* (glucose) 6.4 \pm 2.1 mmol/L; blood CEA mass concentration, *p* (CEA) = 8.6 24.5 μ g/L; CO₂ volume fraction, 50 mL/L CO₂, not 5% CO₂; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.

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