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**Protein kinases is a potential target to treat inflammatory bowel diseases**

Yang L *et al.* Protein kinases is a potential target to treat IBD

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**Abstract**

Protein kinases play a crucial role in the pathogenesis of inflammatory bowel diseases (IBD), mainly ulcerative colitisand Crohn’s disease. In this article, we will review the mechanisms of involvement for protein kinases in the pathogenesis of and intervention against IBD, in the perspectives of their effects in genetics, microbiota, mucous layer and tight junction, and the potential of protein kinases as the target against IBD.

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

**Core tip:** The studies of 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, intend to group these protein kinases into different categories based on their fundamental functions in IBD, and describe substantial new mechanistic insights into the pathogenesis of IBD, which highlight protein kinases as potential intervention target against IBD.

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**INTRODUCTION**

Ulcerative colitis (UC) and Crohn’s disease (CD), two main forms of inflammatory bowel diseases (IBD), are relapsing, idiopathic intestinal inflammatory condition, caused by inappropriate and continuing immunologic responses to aberrant intestinal microorganisms in genetically susceptible individuals under certain environmental conditions[[1](#_ENREF_1)].

UC and CD differ[[2](#_ENREF_2)] with each other dramatically with different respects, for instance, UC is confined to the superficial area of intestinal wall, whereas CD is transmurally distributed around 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 in CD; UC displays Th2-like immunoresponse, and CD is a Th1 dominant response. Further, as autoimmune diseases, antineutrophil cytoplasmic antibodies were found in 65% UC and 5%-10% CD; and Antibodies to yeast S. cerevisiae found in 60%-70% CD and 10%-15% UC[[3](#_ENREF_3)]. Meanwhile, UC and CD share a lot of inflammatory similarities, such as histologically neutrophil infiltration and epithelial barrier dysfunction. Even though the fact that there is no cure for IBD thus far, enormous progresses about the pathogenic mechanisms of this inflammatory disorder have been around the corner in different aspects, such as in aspects of genetics, regulatory immunology and microbiome *etc.*

The signaling pathways mediated by protein kinases have drawn a lot attention for connecting external stimuli including hostile environmental stresses and internal biological responses, such as intestinal inflammation. Protein kinases can be defined as enzymes which add phosphate (called phosphorylation) to the side chain of serine, threonine or tyrosine of substrate molecules which modifies the biological function of the substrate, such as changing enzyme activity, cellular distribution, further causing diseases[[4](#_ENREF_4),[5](#_ENREF_5)]. In this review, we will shed light on the roles of protein kinases in the pathogenic mechanisms of intestinal inflammation and describe substantial some new mechanistic insights into the intervention of IBD, which targets at protein kinases.

**PROTEIN KINASE AND GENETIC FACTORS**

Genome-wide association studies (GWAS) demonstrated that genetic factors are very crucial in the individual susceptibility of IBD, for example, UC relatives including twins display almost ten times greater of risk than non-relatives[[6](#_ENREF_6),[7](#_ENREF_7)]. Further, as shown in Table 1, major IBD susceptibility regions on chromosome 16 and 6 contain some genes encoding protein kinases like extracellular signals-regulated kinase 1(ERK1)[[8](#_ENREF_8)] and p38[[9](#_ENREF_9)]. Several single-nucleotide polymorphisms (SNPs) in tyrosine kinase 2 (TYK2)[[10](#_ENREF_10)] and janus kinase 2 (JAK2)[[11](#_ENREF_11)] were identified from IBD patients. Glucokinase regulator (GCKR) has also been associated with the risk of CD[[12](#_ENREF_12)]. The Cyclin-dependent kinase 5 regulatory subunit-associated protein 1-like (CDKAL1) plays an important role in the susceptibility of CD, Psoriasis and type 11 diabetes[[13](#_ENREF_13),[14](#_ENREF_14)]; Leucine-rich repeat kinase 2 *(*LRRK2) is identified to be related to the pathogenesis of CD[[15](#_ENREF_15)].

**PROTEIN KINASE AND MICROBIOTA**

Up to 1014 individual bacteria in human gastrointestinal (GI) tract[[16](#_ENREF_16)], together with mucous layer where the microbiome lives in, constitutes the first line of defense in host against hostile external environment, modulating GI tract development, maintain immune homeostasis, and regulating host metabolism rate. The bacteria abnormality plays a dominant role in the onset and development of IBD.

Commensal bacteria and host innate immune system evolve together, by thus maintain mucosal immune homeostasis by balancing inflammatory responses and regulating variety of bacteria-triggering signal transduction pathways[[17](#_ENREF_17)], such as uncoupling NF-κB or MAPK dependent target genes in a negative feedback manner[[18](#_ENREF_18),[19](#_ENREF_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 (PAMPs) can wake up the host innate immune system[[20](#_ENREF_20), [21](#_ENREF_21)], which can 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 (NLR)[[22](#_ENREF_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, then, the activated MAPK undergoes translocation to the nucleus to activate molecules required for genes transcription, including inflammatory molecules[[23](#_ENREF_23),[24](#_ENREF_24)]. For example, anthrax toxin can induce macrophage death by inhibiting p38 signaling pathway[[25](#_ENREF_25),[26](#_ENREF_26)]; MAPK-activated protein kinase 2 plays an important role in the pathogenesis of Clostridium difficile-associated intestinal inflammation[[27](#_ENREF_27)]. For NF-κB pathway, after being activated by IκB kinase kinase (IKK) complex, it phosphorylates α subunit of IκB, the inhibitor of NF-κB. Phosphorylation of IκB, accompanying its ubiquitination and proteolytic degradation, results in exposure of the nuclear localization signals (NLS) on the now unbound NF-κB[[28](#_ENREF_28)], which will further facilitate nuclear translocation of NF-κB and followed by many genes transcriptional activation. In addition, even being regarded as an molecule which can promote inflammatory responses, an anti-inflammatory reaction of NF-κB was noticed; absence of NEMO kinase causes spontaneous severe colitis, but commensal bacteria can stimulate NF-κB pathway to protect the host from exacerbating consequence[[29](#_ENREF_29)]. Blockage of epithelial NF-κB pathway will deteriorate this colitis by increasing the translocation of bacterial to mucosa[[30](#_ENREF_30)]. Besides MAPK and NF-κB pathways, some other signaling pathway 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 and tight the epithelial barrier[[31](#_ENREF_31)]. However, PI3 kinase signaling promotes Campylobacter jejunum-induced colitis through neutrophil recruitment in mice[[32](#_ENREF_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](#_ENREF_33)]. Not like NOD2 whose signaling induces cryptidins, MyD88-mediated TLR induces RegIIIg and α-defensins, and more importantly, regulates bacterial-related mucosal immunity[[34-36](#_ENREF_34)]. In parallel, protein kinase C (PKC) can mediate the function of MyD88 adaptor-like (Mal) molecule in the maintenance of epithelial barrier integrity[[37](#_ENREF_37)].

**PROTEIN KINASE 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 to regulate 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, together with commensal bacteria constitutes a physical barrier between epithelium and luminal contents including pathogenic bacteria, viruses, and parasites[[38](#_ENREF_38),[39](#_ENREF_39)]. This gel-like mucus layer can be divided by two distinguished layers-the outer and inner layer. The vast intestinal bacteria, virus and even parasites live in 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 amount of defensins, cathelicidiens, and cryptidens with important function of anti-intestinal pathogens. Mucin coding gene muc2-/- mice demonstrated spontaneous colitis because of increased transepithelial permeability[[40](#_ENREF_40)], in which bacteria can stick to the surface of intestinal mucosa, which facilitates the translocation of bacteria into lower crypts and epithelial cells, then triggering an inflammatory response[[39](#_ENREF_39),[41](#_ENREF_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](#_ENREF_42),[43](#_ENREF_43)]. After stimulating by transforming growth factor alpha (TGF-a) and epidermal growth factor (EGF)-EGFR ligands, epithelial cells can develop into a mucous phenotype[[44](#_ENREF_44),[45](#_ENREF_45)]. However, inhibition of EGFR tyrosine kinase activity can abolish the effects of EGFR ligands on mucus production both *in vivo* and *in vitro*. PKCδ stimulates the secretion of mucin in epithelium *via* regulation of myristoylated alanine-rich protein kinaseC substrate (MARCKS) pathway[[46](#_ENREF_46)]. Treatment by PD98059 (MEK inhibitor) on epithelial cells can inhibit MAPK activity, further block the expression of terminal differentiation markers, such as sucrase-isomaltase, ITF, and MUC2, interfering with the production of mucin[[47](#_ENREF_47)]. Some kinases like extracellular signal-regulated kinases (ERKs), TK, and PKC[[48](#_ENREF_48)] can regulate the production of mucin by mediating the activity of resistin and resistin-like molecule (RELM)-beta; Cathelicidin up-regulates MUC1 and MUC2 expression through MAPK pathway to modulate mucus synthesis[[49](#_ENREF_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](#_ENREF_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](#_ENREF_50)]. Occludin, as the first identified TJ[[51](#_ENREF_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](#_ENREF_52)]. The claudins, as a group of TJ proteins with approximately 24 members, interacts with numbers of other cell structures and affects junctional function[[55-58](#_ENREF_55)]. The expression of claudins harbors a tissue-specific manner and with distinguished function, for example, in colon are expressed the claudins-1, 2, 3, 4, 5, 7, and 8, meanwhile, the claudin-2 is a pore-forming TJ protein, but claudin-1 and 4 are barrier tightening proteins[[59-63](#_ENREF_59)]. 12-O-tetradecanoylophorbol-13-acetate (TPA) can increase transepithelial electrical resistance (TER) by activating different isoforms of protein kinase C (PKC) and enhancing the expression of TJ proteins ZO-1, 2, occludin and claudin-1[[64](#_ENREF_64),[65](#_ENREF_65)]. Ca2+/calmodulin-dependent protein kinase II (CaM kinase II) can compromise endothelial barrier function[[66](#_ENREF_66)]. Ras-transfected epithelial cells demonstrated compromised barrier function, however, the inhibition of MAPK signaling pathway can restore the morphology of epithelial cells and the TJ assembly. Further, the phosphorylation of tyrosine in occludin and ZO-1 may be crucial in the formation of TJ[[67](#_ENREF_67)]. cAMP-dependent protein kinases regulate epithelial barrier function by phosphorylation of claudin-3[[68](#_ENREF_68),[69](#_ENREF_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](#_ENREF_70)]. The size-selectivity related paracellular pathway is one of the two routes, which facilitates transepithelial passage of different size of molecules, such as lipopolysaccharides (LPS)[[71](#_ENREF_71),[72](#_ENREF_72)], which can be regulated by protein kinases, such as MAPKs, SPAK[[73](#_ENREF_73)], protein kinase C (PKC)[[64](#_ENREF_64),[65](#_ENREF_65)] and myosin light chain kinase (MLCK)[[74](#_ENREF_74)]. Another route, also called charge-selectivity route, is composed of pore-forming proteins claudins[[75-77](#_ENREF_75)]. Dysfunction of these two routes, either in size-dependent pathway or in 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, virus and parasites with host 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 mucus layer, microbiota and epithelial cell itself mentioned above, genetic factors play crucial roles in the regulation of intestinal barrier function[[6](#_ENREF_6)]; innate and adaptive immune system can interfere with epithelial permeability in a dramatic manner[[78](#_ENREF_78)]; autonomic nerves, like enteric glial nerve ablation, can perish epithelial permeability to develop fulminant jejunoileitis[[79](#_ENREF_79)]. However, barrier dysfunction itself, like in MLCK[[74](#_ENREF_74)] and SPAK[[73](#_ENREF_73)] gene modified mice, does not necessarily mean that the mice is destined to intestinal inflammation, implying formidable compensation in host.

**PROTEIN KINASE AND PATHOGENESIS OF IBD**

***Mitogen activated protein kinases***

Notably, protein kinases play very crucial roles in many aspects of pathogenesis of IBD, causing emerging attentions as potential therapeutic targets against IBD. Besides NF-κB pathway, the Mitogen activated protein kinases (MAPK) signaling pathway is another highlighted pathway involved in many different diseases including IBD[[80](#_ENREF_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 (APs), Ets-1, Elk and c-myc. Interestingly, ERK1/2, by the 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 progress, by regulating some pro-inflammatory mediators ( such as interleukin-1) related signaling transductions[[81](#_ENREF_81),[82](#_ENREF_82)], evidenced by their enhance expression and phyosphorylation status during IBD[[83](#_ENREF_83),[84](#_ENREF_84)]. Further, the “tightening” junction protein claudin-4 which plays an important role in epithelial barrier function, is regulated by protein kinase ERK[[85](#_ENREF_85)]. By inducing Akt but blocking p38 signalings, Lactobacillus GG (LGG) prevents cytokine-induced apoptosis in intestinal epithelial cells, indicating p38 and Akt as key mediators of epithelial barrier function[[86](#_ENREF_86),[87](#_ENREF_87)]. p38 activity is increased significantly in tissue from IBD patient and in mouse model of colitis[[83](#_ENREF_83),[84](#_ENREF_84),[88](#_ENREF_88)], in which inhibition of p38 lowers KC (IL-8) and IL-6 production. 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](#_ENREF_89)]. JNK1/2 kinase activity was enhanced in IBD inflamed tissue and blockage of JNK1/2 in experimental colitis will reduce the production of proinflammatoy cytokines[[84](#_ENREF_84),[90](#_ENREF_90),[91](#_ENREF_91)].

**Serine and threonine kinase**

**SPAK**: SPAK is a serine/threonine kinase containing an N-terminal series of proline and alanine repeats (PAPA box) followed by a kinase domain, a nuclear localization signal, a consensus caspase cleavage motif, and a C-terminal regulatory region [[92](#_ENREF_92)]. Colonic SPAK presents as a unique isoform that lacks the PAPA box and F-helix loop in the N-terminus[[93](#_ENREF_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, cell transformation and proliferation, and regulation of chloride transport[[94](#_ENREF_94),[95](#_ENREF_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) that can phosphorylate NKCC1 and play an important role in inflammation[[96](#_ENREF_96)]. Further, we have demonstrated that SPAK can activate p38 pathway[[93](#_ENREF_93)]. Decreased expression of SPAK contributes to the enhanced intestinal barrier, thus its knockout mice were more tolerant to experimental colitis induced by dextran sodium sulphate (DSS) with decreased intestinal microorganism translocation into mucosa and inhibition of the production of inflammatory mediators[[97](#_ENREF_97)].

**MLCK:** MLCK is named after its phosphorylation of MLC to induce contraction of the perijunction actomyosin ring and is indispensable for tumor necrosis factor (TNF) related barrier dysfunction. On parallel, TNF can induce the phosphorylation and transcription of MLCK[[98](#_ENREF_98),[99](#_ENREF_99)]. Constitutive MLCK activation within the intestinal epithelium increases intestinal paracellular permeability and aggravates the severity of mouse model of colitis. However, blockage of MLCK activation can increase significantly the intestinal barrier function and further ameliorate DSS-induced colitis[[100](#_ENREF_100)].

**Protein kinase C:** Protein kinase C (PKC) and its variety of isoforms are involved in the pathogenesis of IBD by their effect on mucus layer[[101](#_ENREF_101)], microbiota[[34-37](#_ENREF_34)], cell junction[[64](#_ENREF_64),[65](#_ENREF_65)] and immune system. Specially, PKCθ plays an important role in T cell receptor (TCR) activation and signaling[[102](#_ENREF_102)] and PKCδ is crucial for B cell tolerance[[103](#_ENREF_103),[104](#_ENREF_104)]. PKC-η can control CTLA-4–mediated Treg cell function[[105](#_ENREF_105)]; however, PKC-Ɵ inhibits Treg function, implying its blocking of Treg-mediated suppression. Inhibition of PKC-Ɵ stimulates Treg, and resumes compromised Treg function in rheumatoid arthritis patients, and enhances protection against experimental colitis in mice, as a result, PKC-Ɵ conducts negative feedback on Treg cell function[[106](#_ENREF_106)].

**CONCLUSION**

Protein kinases and the related signaling transduction pathways are involved in every physiological or pathological process in life such as development, inflammation (for example intestinal inflammation) and tunorigenesis. In this review, we shed some light on the roles of protein kinases in IBD-related genetic factors, microbiota, mucus layer, epithelial cell and the tight junction, we feel imminently that further studies are needed to explore the feasibility and the application of these signaling pathways in the control of IBD.

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Kinases

IBD

Ref.

ERK1

CD

[8]

p38

CD and UC

[9]

TYK2

[10]

CD and UC

JAK2

CD and UC

[11]

GCKR

CD

[12]

CDKAL1

CD

[13]

LRRK2

CD

[15]

Erk1: Extracellar 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.

**Table 1 Protein kinases related to inflammatory bowel diseases genetics**



**Figure 1 Intestinal epithelial cells use 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 factor 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; IKB: 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; AP-1: 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.



**Figure 2 Intestinal Goblet cells employ different mechanisms including protein kinases 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 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; PKCdelta: Protein kinase C delta.