World Journal of Gastrointestinal Pharmacology and Therapeutics

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DOI: 10.4292/wjgpt.v5.i4.209

World J Gastrointest Pharmacol Ther 2014 November 6; 5(4): 209-217
ISSN 2150-5349 (online)

REVIEW

Protein kinases are potential targets to treat inflammatory bowel disease

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Author contributions: Yang L contributed mainly to the revised version of this paper; Yan Y is responsible for designing and writing this paper.
Supported by The Program for Zhejiang Leading Team of Science and Technology Innovation, No. 2011R50021
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Received: December 1, 2013 Revised: April 5, 2014
Accepted: July 27, 2014
Published online: November 6, 2014

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.

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.

Yang L, Yan Y. Protein kinases are potential targets to treat inflammatory bowel disease. *World J Gastrointest Pharmacol Ther* 2014; 5(4): 209-217 Available from: URL: http://www.wjgnet.com/2150-5349/full/v5/i4/209.htm DOI: http://dx.doi.org/10.4292/wjgpt.v5.i4.209

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: 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.

(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

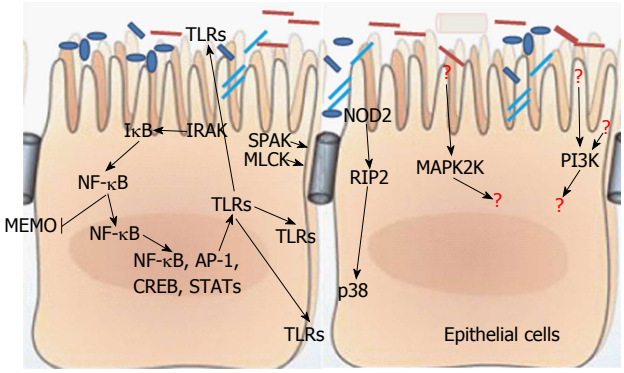

Figure 1 Intestinal epithelial cells use a variety of different molecules including protein kinases to monitor the presence of microbial pathogens, commensal bacteria, or host-generated products. Pathogen-recognition receptors, including TLRs, NOD2, and NLRs, are located on and within the cell where 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 kinase complex, it phosphorylates α subunit of IκB, the inhibitor of NF-κB. Phosphorylation of IκB, accompanied by its ubiquitination and proteolytic degrada-

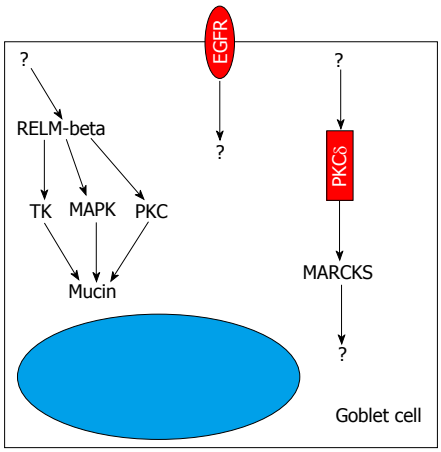

Figure 2 Intestinal Goblet cells employ different mechanisms including protein kinase related pathways to modulate the secretion of mucus, such as pathways related to tyrosine kinase, protein kinase C delta, myristoylated alanine-rich C-kinase substrate or receptors with tyrosine kinase activity such 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-κB[28], which will further facilitate nuclear translocation of NF-κB 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-κB was noticed; absence of NF-κB essential modulator kinase causes spontaneous severe colitis, but commensal bacteria can stimulate the NF-κB pathway to protect the host from exacerbating consequence[29]. Blockage of epithelial NF-κB pathway will deteriorate this colitis by increasing the translocation of bacterial to the mucosa[30]. Besides the MAPK and NF-κB 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 jejunum*-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 cryptdins, 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 cryptidens 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-alpha 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*. PKCδ 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-tetradecanoylophorbol-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]. Ca^{2+}/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-κB 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, PKCθ plays an important role in T cell receptor activation and signaling[102], and PKCδ is crucial for B cell tolerance[103,104]. PKCη 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.

ACKNOWLEDGMENTS

We would thank Miss Ijeoma Okoro, a PhD candidate at Georgia State University, Atlanta, GA, for critically reading the manuscript.

REFERENCES

1 **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]
2 **Abraham C**, Cho JH. Inflammatory bowel disease. *N Engl J Med* 2009; **361**: 2066-2078 [PMID: 19923578 DOI: 10.1056/NEJMra0804647]
3 **Kiliç ZM**, Tunç B, Ayaz S, Filik L, Aktaş S, Parlak E, Ulker A. Antineutrophil cytoplasmic autoantibodies and anti-Saccharomyces cerevisiae antibodies in inflammatory bowel diseases. *Turk J Gastroenterol* 2004; **15**: 238-242 [PMID: 16249978]
4 **Manning G**, Whyte DB, Martinez R, Hunter T, Sudarsanam S. The protein kinase complement of the human genome. *Science* 2002; **298**: 1912-1934 [PMID: 12471243 DOI: 10.1126/science.1075762]
5 **Krachler AM**, Woolery AR, Orth K. Manipulation of kinase signaling by bacterial pathogens. *J Cell Biol* 2011; **195**: 1083-1092 [PMID: 22123833 DOI: 10.1083/jcb.201107132]
6 **Cho JH**, Brant SR. Recent insights into the genetics of inflammatory bowel disease. *Gastroenterology* 2011; **140**: 1704-1712 [PMID: 21530736 DOI: 10.1053/j.gastro.2011.02.046]
7 **Rivas MA**, Beaudoin M, Gardet A, Stevens C, Sharma Y, Zhang CK, Boucher G, Ripke S, Ellinghaus D, Burtt N, Fennell T, Kirby A, Latiano A, Goyette P, Green T, Halfvarson J, Haritunians T, Korn JM, Kuruvilla F, Lagacé C, Neale B, Lo KS, Schumm P, Törkvist L, Dubinsky MC, Brant SR, Silverberg MS, Duerr RH, Altshuler D, Gabriel S, Lettre G, Franke A, D'Amato M, McGovern DP, Cho JH, Rioux JD, Xavier RJ, Daly MJ. Deep resequencing of GWAS loci identifies independent rare variants associated with inflammatory bowel disease. *Nat Genet* 2011; **43**: 1066-1073 [PMID: 21983784 DOI: 10.1038/ng.952]
8 **Hugot JP**, Laurent-Puig P, Gower-Rousseau C, Olson JM, Lee JC, Beaugerie L, Naom I, Dupas JL, Van Gossum A, Orholm M, Bonaiti-Pellie C, Weissenbach J, Mathew CG, Lennard-Jones JE, Cortot A, Colombel JF, Thomas G. Mapping of a susceptibility locus for Crohn's disease on chromosome 16. *Nature* 1996; **379**: 821-823 [PMID: 8587604 DOI: 10.1038/379821a0]
9 **Hampe J**, Shaw SH, Saiz R, Leysens N, Lantermann A, Mascheretti S, Lynch NJ, MacPherson AJ, Bridger S, van Deventer S, Stokkers P, Morin P, Mirza MM, Forbes A, Lennard-Jones JE, Mathew CG, Curran ME, Schreiber S. Linkage of inflammatory bowel disease to human chromosome 6p. *Am J Hum Genet* 1999; **65**: 1647-1655 [PMID: 10577918 DOI: 10.1086/302677]
10 **Khor B**, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. *Nature* 2011; **474**: 307-317 [PMID: 21677747 DOI: 10.1038/nature10209]
11 **Polgar N**, Csongei V, Szabo M, Zambo V, Melegh BI, Sumegi K, Nagy G, Tulassay Z, Melegh B. Investigation of JAK2, STAT3 and CCR6 polymorphisms and their gene-gene interactions in inflammatory bowel disease. *Int J Immunogenet* 2012; **39**: 247-252 [PMID: 22269120 DOI: 10.1111/j.1744-313X.2012.01084.x]
12 **Franke A**, McGovern DP, Barrett JC, Wang K, Radford-Smith GL, Ahmad T, Lees CW, Balschun T, Lee J, Roberts R, Anderson CA, Bis JC, Bumpstead S, Ellinghaus D, Festen EM, Georges M, Green T, Haritunians T, Jostins L, Latiano A, Mathew CG, Montgomery GW, Prescott NJ, Raychaudhuri S, Rotter JI, Schumm P, Sharma Y, Simms LA, Taylor KD, Whiteman D, Wijmenga C, Baldassano RN, Barclay M, Bayless TM, Brand S, Büning C, Cohen A, Colombel JF, Cottone M, Stronati L, Denson T, De Vos M, D'Inca R, Dubinsky M, Edwards C, Florin T, Franchimont D, Gearry R, Glas J, Van Gossum A, Guthery SL, Halfvarson J, Verspaget HW, Hugot JP, Karban A, Laukens D, Lawrance I, Lemann M, Levine A, Libioulle C, Louis E, Mowat C, Newman W, Panés J, Phillips A, Proctor DD, Regueiro M, Russell R, Rutgeerts P, Sanderson J, Sans M, Seibold F, Steinhart AH, Stokkers PC, Torkvist L, Kullak-Ublick G, Wilson D, Walters T, Targan SR, Brant SR, Rioux JD, D'Amato M, Weersma RK, Kugathasan S, Griffiths AM, Mansfield JC, Vermeire S, Duerr RH, Silverberg MS, Satsangi J, Schreiber S, Cho JH, Annese V, Hakonarson H, Daly MJ, Parkes M. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat Genet* 2010; **42**: 1118-1125 [PMID: 21102463 DOI: 10.1038/ng.717]
13 **Quaranta M**, Burden AD, Griffiths CE, Worthington J, Barker JN, Trembath RC, Capon F. Differential contribution

of CDKAL1 variants to psoriasis, Crohn's disease and type II diabetes. *Genes Immun* 2009; **10**: 654-658 [PMID: 19587699 DOI: 10.1038/gene.2009.51]
14 **Wolf N**, Quaranta M, Prescott NJ, Allen M, Smith R, Burden AD, Worthington J, Griffiths CE, Mathew CG, Barker JN, Capon F, Trembath RC. Psoriasis is associated with pleiotropic susceptibility loci identified in type II diabetes and Crohn disease. *J Med Genet* 2008; **45**: 114-116 [PMID: 17993580 DOI: 10.1136/jmg.2007.053595]
15 **Barrett JC**, Hansoul S, Nicolae DL, Cho JH, Duerr RH, Rioux JD, Brant SR, Silverberg MS, Taylor KD, Barmada MM, Bitton A, Dassopoulos T, Datta LW, Green T, Griffiths AM, Kistner EO, Murtha MT, Regueiro MD, Rotter JI, Schumm LP, Steinhart AH, Targan SR, Xavier RJ, Libioulle C, Sandor C, Lathrop M, Belaiche J, Dewit O, Gut I, Heath S, Laukens D, Mni M, Rutgeerts P, Van Gossum A, Zelenika D, Franchimont D, Hugot JP, de Vos M, Vermeire S, Louis E, Cardon LR, Anderson CA, Drummond H, Nimmo E, Ahmad T, Prescott NJ, Onnie CM, Fisher SA, Marchini J, Ghori J, Bumpstead S, Gwilliam R, Tremelling M, Deloukas P, Mansfield J, Jewell D, Satsangi J, Mathew CG, Parkes M, Georges M, Daly MJ. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nat Genet* 2008; **40**: 955-962 [PMID: 18587394 DOI: 10.1038/ng.175]
16 **Qin J**, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, Nielsen T, Pons N, Levenez F, Yamada T, Mende DR, Li J, Xu J, Li S, Li D, Cao J, Wang B, Liang H, Zheng H, Xie Y, Tap J, Lepage P, Bertalan M, Batto JM, Hansen T, Le Paslier D, Linneberg A, Nielsen HB, Pelletier E, Renault P, Sicheritz-Ponten T, Turner K, Zhu H, Yu C, Li S, Jian M, Zhou Y, Li Y, Zhang X, Li S, Qin N, Yang H, Wang J, Brunak S, Doré J, Guarner F, Kristiansen K, Pedersen O, Parkhill J, Weissenbach J, Bork P, Ehrlich SD, Wang J. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* 2010; **464**: 59-65 [PMID: 20203603 DOI: 10.1038/nature08821]
17 **Neish AS**, Gewirtz AT, Zeng H, Young AN, Hobert ME, Karmali V, Rao AS, Madara JL. Prokaryotic regulation of epithelial responses by inhibition of IkappaB-alpha ubiquitination. *Science* 2000; **289**: 1560-1563 [PMID: 10968793]
18 **Dubuquoy L**, Jansson EA, Deeb S, Rakotobe S, Karoui M, Colombel JF, Auwerx J, Pettersson S, Desreumaux P. Impaired expression of peroxisome proliferator-activated receptor gamma in ulcerative colitis. *Gastroenterology* 2003; **124**: 1265-1276 [PMID: 12730867]
19 **Kelly D**, Campbell JI, King TP, Grant G, Jansson EA, Coutts AG, Pettersson S, Conway S. Commensal anaerobic gut bacteria attenuate inflammation by regulating nuclear-cytoplasmic shuttling of PPAR-gamma and RelA. *Nat Immunol* 2004; **5**: 104-112 [PMID: 14691478 DOI: 10.1038/ni1018]
20 **Lemaitre B**, Nicolas E, Michaut L, Reichhart JM, Hoffmann JA. The dorsoventral regulatory gene cassette spätzle/Toll/cactus controls the potent antifungal response in Drosophila adults. *Cell* 1996; **86**: 973-983 [PMID: 8808632]
21 **Medzhitov R**, Janeway CA. Decoding the patterns of self and nonself by the innate immune system. *Science* 2002; **296**: 298-300 [PMID: 11951031 DOI: 10.1126/science.1068883]
22 **Medzhitov R**, Preston-Hurlburt P, Janeway CA. A human homologue of the Drosophila Toll protein signals activation of adaptive immunity. *Nature* 1997; **388**: 394-397 [PMID: 9237759 DOI: 10.1038/41131]
23 **Zheng CF**, Guan KL. Cytoplasmic localization of the mitogen-activated protein kinase activator MEK. *J Biol Chem* 1994; **269**: 19947-19952 [PMID: 8051079]
24 **Yan Y**, Merlin D. Ste20-related proline/alanine-rich kinase: a novel regulator of intestinal inflammation. *World J Gastroenterol* 2008; **14**: 6115-6121 [PMID: 18985800]
25 **Park JM**, Greten FR, Li ZW, Karin M. Macrophage apoptosis by anthrax lethal factor through p38 MAP kinase inhibition. *Science* 2002; **297**: 2048-2051 [PMID: 12202685 DOI: 10.1126/science.1073163]
26 **Ali SR**, Timmer AM, Bilgrami S, Park EJ, Eckmann L, Nizet V, Karin M. Anthrax toxin induces macrophage death by p38 MAPK inhibition but leads to inflammasome activation via ATP leakage. *Immunity* 2011; **35**: 34-44 [PMID: 21683629 DOI: 10.1016/j.immuni.2011.04.015]
27 **Bobo LD**, El Feghaly RE, Chen YS, Dubberke ER, Han Z, Baker AH, Li J, Burnham CA, Haslam DB. MAPK-activated protein kinase 2 contributes to Clostridium difficile-associated inflammation. *Infect Immun* 2013; **81**: 713-722 [PMID: 23264053 DOI: 10.1128/IAI.00186-12]
28 **Alkalay I**, Yaron A, Hatzubai A, Orian A, Ciechanover A, Ben-Neriah Y. Stimulation-dependent I kappa B alpha phosphorylation marks the NF-kappa B inhibitor for degradation via the ubiquitin-proteasome pathway. *Proc Natl Acad Sci USA* 1995; **92**: 10599-10603 [PMID: 7479848]
29 **Nenci A**, Becker C, Wullaert A, Gareus R, van Loo G, Danese S, Huth M, Nikolaev A, Neufert C, Madison B, Gumucio D, Neurath MF, Pasparakis M. Epithelial NEMO links innate immunity to chronic intestinal inflammation. *Nature* 2007; **446**: 557-561 [PMID: 17361131 DOI: 10.1038/nature05698]
30 **Fukata M**, Chen A, Klepper A, Krishnareddy S, Vamadevan AS, Thomas LS, Xu R, Inoue H, Arditi M, Dannenberg AJ, Abreu MT. Cox-2 is regulated by Toll-like receptor-4 (TLR4) signaling: Role in proliferation and apoptosis in the intestine. *Gastroenterology* 2006; **131**: 862-877 [PMID: 16952555 DOI: 10.1053/j.gastro.2006.06.017]
31 **Oppong GO**, Rapsinski GJ, Newman TN, Nishimori JH, Biesecker SG, Tükel Ç. Epithelial cells augment barrier function via activation of the Toll-like receptor 2/phosphatidylinositol 3-kinase pathway upon recognition of Salmonella enterica serovar Typhimurium curli fibrils in the gut. *Infect Immun* 2013; **81**: 478-486 [PMID: 23208603 DOI: 10.1128/IAI.00453-12]
32 **Sun X**, Liu B, Sartor RB, Jobin C. Phosphatidylinositol 3-kinase-γ signaling promotes Campylobacter jejuni-induced colitis through neutrophil recruitment in mice. *J Immunol* 2013; **190**: 357-365 [PMID: 23180818 DOI: 10.4049/jimmunol.1201825]
33 **Homer CR**, Kabi A, Marina-García N, Sreekumar A, Nesvizhskii AI, Nickerson KP, Chinnaiyan AM, Nuñez G, McDonald C. A dual role for receptor-interacting protein kinase 2 (RIP2) kinase activity in nucleotide-binding oligomerization domain 2 (NOD2)-dependent autophagy. *J Biol Chem* 2012; **287**: 25565-25576 [PMID: 22665475 DOI: 10.1074/jbc.M111.326835]
34 **Maloy KJ**, Powrie F. Intestinal homeostasis and its breakdown in inflammatory bowel disease. *Nature* 2011; **474**: 298-306 [PMID: 21677746 DOI: 10.1038/nature10208]
35 **Frantz AL**, Rogier EW, Weber CR, Shen L, Cohen DA, Fenton LA, Bruno ME, Kaetzel CS. Targeted deletion of MyD88 in intestinal epithelial cells results in compromised antibacterial immunity associated with downregulation of polymeric immunoglobulin receptor, mucin-2, and antibacterial peptides. *Mucosal Immunol* 2012; **5**: 501-512 [PMID: 22491177 DOI: 10.1038/mi.2012.23]
36 **Kobayashi KS**, Chamaillard M, Ogura Y, Henegariu O, Inohara N, Nuñez G, Flavell RA. Nod2-dependent regulation of innate and adaptive immunity in the intestinal tract. *Science* 2005; **307**: 731-734 [PMID: 15692051 DOI: 10.1126/science.1104911]
37 **Corr SC**, Palsson-McDermott EM, Grishina I, Barry SP, Aviello G, Bernard NJ, Casey PG, Ward JB, Keely SJ, Dandekar S, Fallon PG, O'Neill LA. MyD88 adaptor-like (Mal) functions in the epithelial barrier and contributes to intestinal integrity via protein kinase C. *Mucosal Immunol* 2014; **7**: 57-67 [PMID: 23612054 DOI: 10.1038/mi.2013.24]
38 **Khan WI**. Physiological changes in the gastrointestinal tract and host protective immunity: learning from the mouse-Trichinella spiralis model. *Parasitology* 2008; **135**: 671-682

[PMID: 18501042 DOI: 10.1017/S0031182008004381]
39 **Johansson ME**, Phillipson M, Petersson J, Velcich A, Holm L, Hansson GC. The inner of the two Muc2 mucin-dependent mucus layers in colon is devoid of bacteria. *Proc Natl Acad Sci USA* 2008; **105**: 15064-15069 [PMID: 18806221 DOI: 10.1073/pnas.0803124105]
40 **Bergstrom KS**, Kissoon-Singh V, Gibson DL, Ma C, Montero M, Sham HP, Ryz N, Huang T, Velcich A, Finlay BB, Chadee K, Vallance BA. Muc2 protects against lethal infectious colitis by disassociating pathogenic and commensal bacteria from the colonic mucosa. *PLoS Pathog* 2010; **6**: e1000902 [PMID: 20485566 DOI: 10.1371/journal.ppat.1000902]
41 **Shen L**, Su L, Turner JR. Mechanisms and functional implications of intestinal barrier defects. *Dig Dis* 2009; **27**: 443-449 [PMID: 19897958 DOI: 10.1159/000233282]
42 **Burgel PR**, Nadel JA. Roles of epidermal growth factor receptor activation in epithelial cell repair and mucin production in airway epithelium. *Thorax* 2004; **59**: 992-996 [PMID: 15516478 DOI: 10.1136/thx.2003.018879]
43 **Hackel PO**, Zwick E, Prenzel N, Ullrich A. Epidermal growth factor receptors: critical mediators of multiple receptor pathways. *Curr Opin Cell Biol* 1999; **11**: 184-189 [PMID: 10209149]
44 **Takeyama K**, Dabbagh K, Lee HM, Agustí C, Lausier JA, Ueki IF, Grattan KM, Nadel JA. Epidermal growth factor system regulates mucin production in airways. *Proc Natl Acad Sci USA* 1999; **96**: 3081-3086 [PMID: 10077640]
45 **Shatos MA**, Gu J, Hodges RR, Lashkari K, Dartt DA. ERK/p44p42 mitogen-activated protein kinase mediates EGF-stimulated proliferation of conjunctival goblet cells in culture. *Invest Ophthalmol Vis Sci* 2008; **49**: 3351-3359 [PMID: 18421078 DOI: 10.1167/iovs.08-1677]
46 **Park JA**, Crews AL, Lampe WR, Fang S, Park J, Adler KB. Protein kinase C delta regulates airway mucin secretion via phosphorylation of MARCKS protein. *Am J Pathol* 2007; **171**: 1822-1830 [PMID: 18055557 DOI: 10.2353/ajpath.2007.070318]
47 **Taupin D**, Podolsky DK. Mitogen-activated protein kinase activation regulates intestinal epithelial differentiation. *Gastroenterology* 1999; **116**: 1072-1080 [PMID: 10220499]
48 **Krimi RB**, Kotelevets L, Dubuquoy L, Plaisancié P, Walker F, Lehy T, Desreumaux P, Van Seuningen I, Chastre E, Forgue-Lafitte ME, Marie JC. Resistin-like molecule beta regulates intestinal mucous secretion and curtails TNBS-induced colitis in mice. *Inflamm Bowel Dis* 2008; **14**: 931-941 [PMID: 18300276 DOI: 10.1002/ibd.20420]
49 **Tai EK**, Wong HP, Lam EK, Wu WK, Yu L, Koo MW, Cho CH. Cathelicidin stimulates colonic mucus synthesis by up-regulating MUC1 and MUC2 expression through a mitogen-activated protein kinase pathway. *J Cell Biochem* 2008; **104**: 251-258 [PMID: 18059019 DOI: 10.1002/jcb.21615]
50 **Mitic LL**, Anderson JM. Molecular architecture of tight junctions. *Annu Rev Physiol* 1998; **60**: 121-142 [PMID: 9558457 DOI: 10.1146/annurev.physiol.60.1.121]
51 **Furuse M**, Hirase T, Itoh M, Nagafuchi A, Yonemura S, Tsukita S, Tsukita S. Occludin: a novel integral membrane protein localizing at tight junctions. *J Cell Biol* 1993; **123**: 1777-1788 [PMID: 8276896]
52 **Yu AS**, McCarthy KM, Francis SA, McCormack JM, Lai J, Rogers RA, Lynch RD, Schneeberger EE. Knockdown of occludin expression leads to diverse phenotypic alterations in epithelial cells. *Am J Physiol Cell Physiol* 2005; **288**: C1231-C1241 [PMID: 15689410 DOI: 10.1152/ajpcell.00581.2004]
53 **Suzuki T**, Elias BC, Seth A, Shen L, Turner JR, Giorgianni F, Desiderio D, Guntaka R, Rao R. PKC eta regulates occludin phosphorylation and epithelial tight junction integrity. *Proc Natl Acad Sci USA* 2009; **106**: 61-66 [PMID: 19114660 DOI: 10.1073/pnas.0802741106]
54 **Elias BC**, Suzuki T, Seth A, Giorgianni F, Kale G, Shen L, Turner JR, Naren A, Desiderio DM, Rao R. Phosphorylation of Tyr-398 and Tyr-402 in occludin prevents its interaction with ZO-1 and destabilizes its assembly at the tight junctions. *J Biol Chem* 2009; **284**: 1559-1569 [PMID: 19017651 DOI: 10.1074/jbc.M804783200]
55 **Van Itallie CM**, Fanning AS, Anderson JM. Reversal of charge selectivity in cation or anion-selective epithelial lines by expression of different claudins. *Am J Physiol Renal Physiol* 2003; **285**: F1078-F1084 [PMID: 13129853 DOI: 10.1152/ajprenal.00116.2003]
56 **Van Itallie CM**, Anderson JM. The molecular physiology of tight junction pores. *Physiology* (Bethesda) 2004; **19**: 331-338 [PMID: 15546850 DOI: 10.1152/physiol.00027.2004]
57 **Van Itallie CM**, Anderson JM. Claudins and epithelial paracellular transport. *Annu Rev Physiol* 2006; **68**: 403-429 [PMID: 16460278 DOI: 10.1146/annurev.physiol.68.040104.131404]
58 **Furuse M**, Tsukita S. Claudins in occluding junctions of humans and flies. *Trends Cell Biol* 2006; **16**: 181-188 [PMID: 16537104 DOI: 10.1016/j.tcb.2006.02.006]
59 **Bürgel N**, Bojarski C, Mankertz J, Zeitz M, Fromm M, Schulzke JD. Mechanisms of diarrhea in collagenous colitis. *Gastroenterology* 2002; **123**: 433-443 [PMID: 12145796]
60 **Escaffit F**, Boudreau F, Beaulieu JF. Differential expression of claudin-2 along the human intestine: Implication of GATA-4 in the maintenance of claudin-2 in differentiating cells. *J Cell Physiol* 2005; **203**: 15-26 [PMID: 15389642 DOI: 10.1002/jcp.20189]
61 **Szakál DN**, Gyorffy H, Arató A, Cseh A, Molnár K, Papp M, Dezsofi A, Veres G. Mucosal expression of claudins 2, 3 and 4 in proximal and distal part of duodenum in children with coeliac disease. *Virchows Arch* 2010; **456**: 245-250 [PMID: 20143085 DOI: 10.1007/s00428-009-0879-7]
62 **Wang N**, Yu H, Ma J, Wu W, Zhao D, Shi X, Tian H, Jiang H. Evidence for tight junction protein disruption in intestinal mucosa of malignant obstructive jaundice patients. *Scand J Gastroenterol* 2010; **45**: 191-199 [PMID: 20095884 DOI: 10.3109/00365520903406701]
63 **Zeissig S**, Bürgel N, Günzel D, Richter J, Mankertz J, Wahnschaffe U, Kroesen AJ, Zeitz M, Fromm M, Schulzke JD. Changes in expression and distribution of claudin 2, 5 and 8 lead to discontinuous tight junctions and barrier dysfunction in active Crohn's disease. *Gut* 2007; **56**: 61-72 [PMID: 16822808 DOI: 10.1136/gut.2006.094375]
64 **Koizumi J**, Kojima T, Ogasawara N, Kamekura R, Kurose M, Go M, Harimaya A, Murata M, Osanai M, Chiba H, Himi T, Sawada N. Protein kinase C enhances tight junction barrier function of human nasal epithelial cells in primary culture by transcriptional regulation. *Mol Pharmacol* 2008; **74**: 432-442 [PMID: 18477669 DOI: 10.1124/mol.107.043711]
65 **Banan A**, Zhang LJ, Shaikh M, Fields JZ, Choudhary S, Forsyth CB, Farhadi A, Keshavarzian A. theta Isoform of protein kinase C alters barrier function in intestinal epithelium through modulation of distinct claudin isotypes: a novel mechanism for regulation of permeability. *J Pharmacol Exp Ther* 2005; **313**: 962-982 [PMID: 15900076 DOI: 10.1124/jpet.104.083428]
66 **Wang Z**, Ginnan R, Abdullaev IF, Trebak M, Vincent PA, Singer HA. Calcium/Calmodulin-dependent protein kinase II delta 6 (CaMKIIdelta6) and RhoA involvement in thrombin-induced endothelial barrier dysfunction. *J Biol Chem* 2010; **285**: 21303-21312 [PMID: 20442409 DOI: 10.1074/jbc.M110.120790]
67 **Chen Yh**, Lu Q, Schneeberger EE, Goodenough DA. Restoration of tight junction structure and barrier function by down-regulation of the mitogen-activated protein kinase pathway in ras-transformed Madin-Darby canine kidney cells. *Mol Biol Cell* 2000; **11**: 849-862 [PMID: 10712504]
68 **D'Souza T**, Agarwal R, Morin PJ. Phosphorylation of claudin-3 at threonine 192 by cAMP-dependent protein kinase regulates tight junction barrier function in ovarian cancer cells. *J Biol Chem* 2005; **280**: 26233-26240 [PMID: 15905176

DOI: 10.1074/jbc.M502003200]
69 **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]
70 **Fihn BM**, Sjöqvist A, Jodal M. Permeability of the rat small intestinal epithelium along the villus-crypt axis: effects of glucose transport. *Gastroenterology* 2000; **119**: 1029-1036 [PMID: 11040189]
71 **Van Itallie CM**, Holmes J, Bridges A, Gookin JL, Coccaro MR, Proctor W, Colegio OR, Anderson JM. The density of small tight junction pores varies among cell types and is increased by expression of claudin-2. *J Cell Sci* 2008; **121**: 298-305 [PMID: 18198187 DOI: 10.1242/jcs.021485]
72 **Watson CJ**, Hoare CJ, Garrod DR, Carlson GL, Warhurst G. Interferon-gamma selectively increases epithelial permeability to large molecules by activating different populations of paracellular pores. *J Cell Sci* 2005; **118**: 5221-5230 [PMID: 16249235 DOI: 10.1242/jcs.02630]
73 **Yan Y**, Laroui H, Ingersoll SA, Ayyadurai S, Charania M, Yang S, Dalmasso G, Obertone TS, Nguyen H, Sitaraman SV, Merlin D. Overexpression of Ste20-related proline/alanine-rich kinase exacerbates experimental colitis in mice. *J Immunol* 2011; **187**: 1496-1505 [PMID: 21705622 DOI: 10.4049/jimmunol.1002910]
74 **Turner JR**. Molecular basis of epithelial barrier regulation: from basic mechanisms to clinical application. *Am J Pathol* 2006; **169**: 1901-1909 [PMID: 17148655 DOI: 10.2353/ajpath.2006.060681]
75 **Amasheh S**, Meiri N, Gitter AH, Schöneberg T, Mankertz J, Schulzke JD, Fromm M. Claudin-2 expression induces cation-selective channels in tight junctions of epithelial cells. *J Cell Sci* 2002; **115**: 4969-4976 [PMID: 12432083]
76 **Colegio OR**, Van Itallie C, Rahner C, Anderson JM. Claudin extracellular domains determine paracellular charge selectivity and resistance but not tight junction fibril architecture. *Am J Physiol Cell Physiol* 2003; **284**: C1346-C1354 [PMID: 12700140 DOI: 10.1152/ajpcell.00547.2002]
77 **Simon DB**, Lu Y, Choate KA, Velazquez H, Al-Sabban E, Praga M, Casari G, Bettinelli A, Colussi G, Rodriguez-Soriano J, McCredie D, Milford D, Sanjad S, Lifton RP. Paracellin-1, a renal tight junction protein required for paracellular Mg2+ resorption. *Science* 1999; **285**: 103-106 [PMID: 10390358]
78 **Fuss IJ**. Is the Th1/Th2 paradigm of immune regulation applicable to IBD? *Inflamm Bowel Dis* 2008; **14** Suppl 2: S110-S112 [PMID: 18816734 DOI: 10.1002/ibd.20683]
79 **Bush TG**, Savidge TC, Freeman TC, Cox HJ, Campbell EA, Mucke L, Johnson MH, Sofroniew MV. Fulminant jejunoileitis following ablation of enteric glia in adult transgenic mice. *Cell* 1998; **93**: 189-201 [PMID: 9568712]
80 **Coskun M**, Olsen J, Seidelin JB, Nielsen OH. MAP kinases in inflammatory bowel disease. *Clin Chim Acta* 2011; **412**: 513-520 [PMID: 21185271 DOI: 10.1016/j.cca.2010.12.020]
81 **Caruso R**, Fina D, Peluso I, Stolfi C, Fantini MC, Gioia V, Caprioli F, Del Vecchio Blanco G, Paoluzi OA, Macdonald TT, Pallone F, Monteleone G. A functional role for interleukin-21 in promoting the synthesis of the T-cell chemoattractant, MIP-3alpha, by gut epithelial cells. *Gastroenterology* 2007; **132**: 166-175 [PMID: 17241869 DOI: 10.1053/j.gastro.2006.09.053]
82 **Kwon KH**, Ohigashi H, Murakami A. Dextran sulfate sodium enhances interleukin-1 beta release via activation of p38 MAPK and ERK1/2 pathways in murine peritoneal macrophages. *Life Sci* 2007; **81**: 362-371 [PMID: 17628610 DOI: 10.1016/j.lfs.2007.05.022]
83 **Waetzig GH**, Seegert D, Rosenstiel P, Nikolaus S, Schreiber S. p38 mitogen-activated protein kinase is activated and linked to TNF-alpha signaling in inflammatory bowel disease. *J Immunol* 2002; **168**: 5342-5351 [PMID: 11994493]
84 **Dahan S**, Roda G, Pinn D, Roth-Walter F, Kamalu O, Martin AP, Mayer L. Epithelial: lamina propria lymphocyte interactions promote epithelial cell differentiation. *Gastroenterology* 2008; **134**: 192-203 [PMID: 18045591 DOI: 10.1053/j.gastro.2007.10.022]
85 **Pinton P**, Braicu C, Nougayrede JP, Laffitte J, Taranu I, Oswald IP. Deoxynivalenol impairs porcine intestinal barrier function and decreases the protein expression of claudin-4 through a mitogen-activated protein kinase-dependent mechanism. *J Nutr* 2010; **140**: 1956-1962 [PMID: 20861219 DOI: 10.3945/jn.110.123919]
86 **Resta-Lenert S**, Barrett KE. Probiotics and commensals reverse TNF-alpha- and IFN-gamma-induced dysfunction in human intestinal epithelial cells. *Gastroenterology* 2006; **130**: 731-746 [PMID: 16530515 DOI: 10.1053/j.gastro.2005.12.015]
87 **Yan F**, Polk DB. Probiotic bacterium prevents cytokine-induced apoptosis in intestinal epithelial cells. *J Biol Chem* 2002; **277**: 50959-50965 [PMID: 12393915 DOI: 10.1074/jbc.M207050200]
88 **Garat C**, Arend WP. Intracellular IL-1Ra type 1 inhibits IL-1-induced IL-6 and IL-8 production in Caco-2 intestinal epithelial cells through inhibition of p38 mitogen-activated protein kinase and NF-kappaB pathways. *Cytokine* 2003; **23**: 31-40 [PMID: 12901852]
89 **Ueno N**, Fujiya M, Segawa S, Nata T, Moriichi K, Tanabe H, Mizukami Y, Kobayashi N, Ito K, Kohgo Y. Heat-killed body of lactobacillus brevis SBC8803 ameliorates intestinal injury in a murine model of colitis by enhancing the intestinal barrier function. *Inflamm Bowel Dis* 2011; **17**: 2235-2250 [PMID: 21987297 DOI: 10.1002/ibd.21597]
90 **Assi K**, Pillai R, Gómez-Muñoz A, Owen D, Salh B. The specific JNK inhibitor SP600125 targets tumour necrosis factor-alpha production and epithelial cell apoptosis in acute murine colitis. *Immunology* 2006; **118**: 112-121 [PMID: 16630028 DOI: 10.1111/j.1365-2567.2006.02349.x]
91 **Mitsuyama K**, Suzuki A, Tomiyasu N, Tsuruta O, Kitazaki S, Takeda T, Satoh Y, Bennett BL, Toyonaga A, Sata M. Pro-inflammatory signaling by Jun-N-terminal kinase in inflammatory bowel disease. *Int J Mol Med* 2006; **17**: 449-455 [PMID: 16465391]
92 **Johnston AM**, Naselli G, Gonez LJ, Martin RM, Harrison LC, DeAizpurua HJ. SPAK, a STE20/SPS1-related kinase that activates the p38 pathway. *Oncogene* 2000; **19**: 4290-4297 [PMID: 10980603 DOI: 10.1038/sj.onc.1203784]
93 **Yan Y**, Nguyen H, Dalmasso G, Sitaraman SV, Merlin D. Cloning and characterization of a new intestinal inflammation-associated colonic epithelial Ste20-related protein kinase isoform. *Biochim Biophys Acta* 2007; **1769**: 106-116 [PMID: 17321610 DOI: 10.1016/j.bbaexp.2007.01.003]
94 **Piechotta K**, Lu J, Delpire E. Cation chloride cotransporters interact with the stress-related kinases Ste20-related proline-alanine-rich kinase (SPAK) and oxidative stress response 1 (OSR1). *J Biol Chem* 2002; **277**: 50812-50819 [PMID: 12386165 DOI: 10.1074/jbc.M208108200]
95 **Gagnon KB**, England R, Delpire E. Characterization of SPAK and OSR1, regulatory kinases of the Na-K-2Cl cotransporter. *Mol Cell Biol* 2006; **26**: 689-698 [PMID: 16382158 DOI: 10.1128/MCB.26.2.689-698.2006]
96 **Topper JN**, Wasserman SM, Anderson KR, Cai J, Falb D, Gimbrone MA. Expression of the bumetanide-sensitive Na-K-Cl cotransporter BSC2 is differentially regulated by fluid mechanical and inflammatory cytokine stimuli in vascular endothelium. *J Clin Invest* 1997; **99**: 2941-2949 [PMID: 9185518 DOI: 10.1172/JCI119489]
97 **Zhang Y**, Viennois E, Xiao B, Baker MT, Yang S, Okoro I, Yan Y. Knockout of Ste20-like proline/alanine-rich kinase (SPAK) attenuates intestinal inflammation in mice. *Am J Pathol* 2013; **182**: 1617-1628 [PMID: 23499375 DOI: 10.1016/j.ajpath.2013.01.028]

98 **Wang F**, Graham WV, Wang Y, Witkowski ED, Schwarz BT, Turner JR. Interferon-gamma and tumor necrosis factor-alpha synergize to induce intestinal epithelial barrier dysfunction by up-regulating myosin light chain kinase expression. *Am J Pathol* 2005; **166**: 409-419 [PMID: 15681825]
99 **Graham WV**, Wang F, Clayburgh DR, Cheng JX, Yoon B, Wang Y, Lin A, Turner JR. Tumor necrosis factor-induced long myosin light chain kinase transcription is regulated by differentiation-dependent signaling events. Characterization of the human long myosin light chain kinase promoter. *J Biol Chem* 2006; **281**: 26205-26215 [PMID: 16835238 DOI: 10.1074/jbc.M602164200]
100 **Clayburgh DR**, Musch MW, Leitges M, Fu YX, Turner JR. Coordinated epithelial NHE3 inhibition and barrier dysfunction are required for TNF-mediated diarrhea in vivo. *J Clin Invest* 2006; **116**: 2682-2694 [PMID: 17016558 DOI: 10.1172/JCI29218]
101 **Larivée P**, Levine SJ, Martinez A, Wu T, Logun C, Shelhamer JH. Platelet-activating factor induces airway mucin release via activation of protein kinase C: evidence for translocation of protein kinase C to membranes. *Am J Respir Cell Mol Biol* 1994; **11**: 199-205 [PMID: 8049080 DOI: 10.1165/ajrcmb.11.2.8049080]
102 **Sun Z**, Arendt CW, Ellmeier W, Schaeffer EM, Sunshine MJ, Gandhi L, Annes J, Petrzilka D, Kupfer A, Schwartzberg PL, Littman DR. PKC-theta is required for TCR-induced NF-kappaB activation in mature but not immature T lymphocytes. *Nature* 2000; **404**: 402-407 [PMID: 10746729 DOI: 10.1038/35006090]
103 **Miyamoto A**, Nakayama K, Imaki H, Hirose S, Jiang Y, Abe M, Tsukiyama T, Nagahama H, Ohno S, Hatakeyama S, Nakayama KI. Increased proliferation of B cells and autoimmunity in mice lacking protein kinase Cdelta. *Nature* 2002; **416**: 865-869 [PMID: 11976687 DOI: 10.1038/416865a]
104 **Mecklenbräuker I**, Saijo K, Zheng NY, Leitges M, Tarakhovsky A. Protein kinase Cdelta controls self-antigen-induced B-cell tolerance. *Nature* 2002; **416**: 860-865 [PMID: 11976686 DOI: 10.1038/416860a]
105 **Kong KF**, Fu G, Zhang Y, Yokosuka T, Casas J, Canonigo-Balancio AJ, Becart S, Kim G, Yates JR, Kronenberg M, Saito T, Gascoigne NR, Altman A. Protein kinase C-η controls CTLA-4-mediated regulatory T cell function. *Nat Immunol* 2014; **15**: 465-472 [PMID: 24705298 DOI: 10.1038/ni.2866]
106 **Zanin-Zhorov A**, Ding Y, Kumari S, Attur M, Hippen KL, Brown M, Blazar BR, Abramson SB, Lafaille JJ, Dustin ML. Protein kinase C-theta mediates negative feedback on regulatory T cell function. *Science* 2010; **328**: 372-376 [PMID: 20339032 DOI: 10.1126/science.1186068]

P- Reviewer: Catania VA, Hou WH, Lambrecht NW
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