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TOPIC HIGHLIGHT

Jamal A Ibdah, MD, PhD, *Series Editor*

Role of the JNK signal transduction pathway in inflammatory bowel disease

Praveen K Roy, Farzana Rashid, Jack Bragg, Jamal A Ibdah

Praveen K Roy, Farzana Rashid, Jack Bragg, Jamal A Ibdah, Division of Gastroenterology and Hepatology, University of Missouri School of Medicine, Columbia, Missouri, United States
Correspondence to: Praveen K Roy, MD, Division of Gastroenterology, Department of Medicine, University of Missouri, DC 043.00, Room 580, One Hospital Drive. Columbia, MO 65212, United States. roypk@health.missouri.edu
Telephone: +1-573-8827758 Fax: +1-573-8844595
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Abstract

The c-Jun NH2-terminal Kinase (JNK) pathway represents one sub-group of the mitogen-activated protein (MAP) kinases which plays an important role in various inflammatory diseases states, including inflammatory bowel disease (IBD). Significant progress towards understanding the function of the JNK signaling pathway has been achieved during the past few years. Blockade of the JNK pathway with JNK inhibitors in animal models of IBD lead to resolution of intestinal inflammation. Current data suggest specific JNK inhibitors hold promise as novel therapies in IBD.

Key words: JNK pathway; Inflammatory bowel disease; Inflammation

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INTRODUCTION

Although our understanding of the pathogenesis of inflammatory bowel disorders (IBD), especially Crohn's disease (CD) and ulcerative colitis (UC) has greatly improved, the specific causes are still not known. Cytokines such as TNF-α, IL-1 and IFN-γ play an important role in the pathogenesis of IBD[1,2]. Elucidating the mechanisms of cytokine induced inflammation in IBD could lead to novel therapies. Recent studies have focused on the identification of intracellular signaling pathways and transcription factors through which cytokines mediate their effects. Mitogen-activated protein kinases (MAPKs) are components of the signaling cascades where diverse extracellular stimuli converge to initiate inflammatory cellular responses. MAPKs are made of three subgroups-p42/44 extracellular signaling kinase (ERK), Jun-N-terminal Kinase (JNK), and p38 MAP Kinase[3]. Recent studies have highlighted the importance of the JNK pathway in IBD. This review will focus on the role of the JNK signaling pathway in IBD.

THE JNK-MAPK PATHWAY

The mammalian JNK were initially called stress activated protein kinase (SAPK) because they were activated by a variety of environmental stresses[3,4]. Later, the JNK pathway was also discovered to respond to cytokines, such as TNF-α and IL-1, and growth factors. JNK is a multi-factorial kinase involved in several physiological and pathological processes. Specific stimuli trigger the activation of MAP3Ks, which then phosphorylate and activate the MAP2K isoforms MKK4 and MKK7, which in turn phosphorylate and activate JNK[5]. JNK was discovered to phosphorylate c-Jun at the NH2-terminal Ser63 and 73 residues, and thus termed JNK. However, several recent studies have shown that JNK can phosphorylate a variety of substrates, including additional transcription factors and some non-nuclear proteins[3,6]. In addition to c-Jun, JNK can phosphorylate transcription factors such as JunB, JunD, c-fos, ATF2 and ATF3. These transcription factors along with c-Jun, make up the Activator Protein-1 transcription factor (AP-1), which regulates the expression of several stress-responsive genes. The JNK class of enzymes comprises of three main types: JNK1, JNK2, and JNK3[4,7]. The first two are ubiquitous, whereas the third is restricted to the brain, heart and testis. Differential splicing and exon usage results in multiple isoforms of JNK1, 2 and 3 genes. Each JNK is expressed as a short form (46 kDa) and long form (54 kDa)[3]. The alternative forms of each JNK1, 2, and 3 appear to differ in their ability of bind and phosphorylate different substrate proteins. Targeted gene disruption of each JNK has also defined differential functions for JNK1, JNK2 and JNK3 in many different cell types[7]. Deletion of JNK1 or JNK2 resulted in defective T cell differentiation and activation[8].

ROLE OF JNK IN IBD

The JNK pathway is considered to be a potentially relevant target for therapy inflammatory disease states. JNK regulates the maturation and activity of T cells and synthesis of pro-inflammatory cytokines such as interleukin-2 (IL-2), IL-6 and TNF-α. Several recent studies have demonstrated the importance of JNK pathway in chronic inflammatory disorders involving the expression of specific proteases and cytokines. For example, JNK pathway appears to be involved in the expression of TNF-α in rheumatoid arthritis[9]. JNK inhibitors such as SP600125 protected mice from joint damage in rheumatoid arthritis animal models[9]. Additionally, the JNK pathway also plays a role in artherosclerosis[10,11]. These findings led to the investigation of the role of JNK pathway in intestinal inflammation.

JNK activation in human intestine in patients with IBD was shown in 4 studies[12,13]. Increased activation of JNK along with ERK and p38 MAPK in human colonic tissue from 27 patients with moderate to severe CD or UC was first shown by Waetzig et al. Hommes *et al* also noted increased activation of p38 and JNK in their study involving 12 patients. Mistsuyama *et al* subsequently confirmed these findings in their recent study. They examined whether JNK phosphorylation was greater in sites of active inflammation compared to normal intestine in patients with IBD. Both ELISA and immunostaining demonstrated that JNK was highly activated in colonic tissue with active disease. Phospho-JNK was present in the intestinal cells, macrophages and lymphocytes, localized pre-dominantly in the nucleus. These findings validated the results from *in-vitro* cell culture studies[14]. Interestingly, increased JNK activation has also been shown in steroid-resistant patients[15]. The significance of this finding is currently unclear. The detection of enhanced activation of JNK in intestinal tissue in patients with IBD may serve as a diagnostic tool for early recognition of steroid unresponsiveness. Role of the different isoforms of JNK in IBD was investigated in a recent study[16]. Deletion of either JNK1 or JNK2 did not prevent the development of colitis in animals. However, deletion of JNK2 was associated with deterioration of disease activity. Further studies examining the role of different isoforms of JNK in IBD are needed.

The role of JNK inhibitors as potential therapies for IBD has been studied in both animal models of IBD and in humans. There are at least 40 different small-molecule JNK inhibitors that have either published or patented[3]. These inhibitors either affect JNK signaling pathway indirectly (e.g. CEP 1347) or block the catalytic domain of JNK (e.g. SP 600125). Unfortunately, most of these compounds only have a moderate specificity for JNK and may also interfere with other signaling pathways. Peptide inhibitors of JNK pathway, which have a higher specificity for their targets, are currently being developed. However, one of the major obstacles with peptide drugs is their rapid degradation and difficulty with delivery across cell membranes. These obstacles have been reportedly overcome by a recently described cell-permeable peptide that contains the JNK-binding domain of human c-Jun. Two studies assessed the effect of JNK inhibitor, SP 600125, on dextran sodium sulphate (DSS) colitis animal model[12,17]. SP 600125 is a reversible ATP-competitive inhibitor of protein kinases. It targets all the three different isoforms of JNK. At higher concentrations, it inhibits other protein kinases upstream of JNK (namely MKK3, and MKK6). One study evaluated SP 600125 in a rat model (Sprague-Dawley rats) of DSS colitis while the other used a mice model (C57BL/6) of DSS colitis. Both studies demonstrated the activation of JNK pathway in inflamed intestinal tissue in DSS induced colitis. JNK inhibition showed a marked protective effect against experimental colonic injury in animals. Specifically, treatment with SP600125 led to attenuation of weight loss and macroscopic damage. A beneficial effect was also noted on the histological severity of colitis. Destruction of the epithelial layer and glandular architecture, inflammatory infiltrates in the lamina propria, and edema of the submucosa in the colon was less severe in the SP600125 treated animals. Treatment with SP 600125 also resulted in a significant reduction in the levels of TNF-α, IL-6 and IFN-γ. Additionally, SP 600125 inhibited cytokine production by activated CD3/CD28 mesenteric lymphocytes[17]. One major limitation of these studies is that a more specific inhibitor of JNK was not investigated. Animal studies utilizing a peptide inhibitor or SiRNA against the JNK pathway are needed. Human studies have also suggested similar benefits of JNK blockade to those seen in animals. CNI-1493, a guanylhydrazone that inhibits the phosphorylation of both JNK and p38 MAP kinase, was studied in an open- label pilot study in 12 patients with moderate to severe Crohn's disease. Two different doses of CNI-1493 (8 or 25 mg/m^2) were given intravenously once daily for 12 d. A significant change in CDAI from baseline was noted at wk 2 and persisted up to wk 16. CRP levels decreased significantly during the first weeks of treatment. Endoscopic improvement was observed in all but one patient. Five patients had active fistulizing CD, and closure of the fistula was observed in 4 patients. A steroid sparing effect was seen in 89% of patients maintained on steroids. Additionally, CD-related arthralgia/arthritis resolved in all patients. Although the small sample size in this study precludes any significant conclusions, this study suggests CNI-1493 has significant therapeutic potential in CD. Further studies using JNK specific inhibitors in IBD are currently needed.

CONCLUSION

The JNK pathway plays an important role in various inflammatory disorders. Recent data suggest that JNK activation plays an important role in the intestinal inflammation in patients with IBD. However, the role of the different JNK isoforms in IBD has not been elucidated. Additionally, the mechanism by which JNK activation leads to intestinal inflammation is unclear and deserves further study. Cross talk of JNK pathway with other signaling pathways also needs to be investigated. Recent studies suggest a role for JNK blockade in IBD therapy. However, JNK inhibitors which could also inhibit other kinases were used. Studies using JNK specific inhibitors (e.g. peptide inhibitors) are needed. To increase

the likelihood of success, it may be important to develop isoform-specific JNK inhibitors, as they are likely to have increased efficacy and specificity resulting in fewer potential side effects.

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