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Cell-Specific Inhibition of p38α as a Therapeutic Strategy for Inflammatory Bowel Disease

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Anti-tumor necrosis factor (TNF) therapies have provided an invaluable therapeutic alternative to immunomodulators, corticosteroids, and mesalamine compounds for the induction and maintenance of remission in inflammatory bowel disease (IBD). However, sustained remission drops significantly at 1 year, and the efficacy of manipulating other cytokines (eg, interleukin [IL]-6, IL-10, and IL-11) has been limited.[1–3] Therefore, there is an unmet need for alternative biological therapies. Restoring the balance of pro- and anti-inflammatory pathways in IBD is a potential strategy that deserves further examination. A prospective novel approach is to target molecular pathways upstream of the proinflammatory cytokines that mediate IBD, such as nuclear factor (NF)-κB and the mitogen activated protein kinases (MAPKs). MAPKs comprise a large family of highly conserved serine/threonine protein kinases implicated in the regulation of a vast array of key cellular processes, such as production of cytokines, migration and accumulation of leukocytes, and angiogenesis, all of which contribute to the pathogenesis of IBD. Because of their key regulatory role in the production of inflammatory cytokines and in mediating their downstream effects, their inhibition has received considerable attention as a novel therapeutic strategy for inflammatory diseases.

In mammals, there are 3 major classes of MAPKs, the extracellular signal-regulated kinases and the 2 stress-activated protein kinase families, c-jun N-terminal kinase (JNK) and p38. The p38 family is composed of 4 isoforms (α, β, γ, and δ). The α, β, and δ isoforms are expressed widely in leukocyte subsets including $CD4^+$ T cells, neutrophils, monocytes, macrophages, and endothelial cells.[4] The p38α isoform has received the most attention as a therapeutic target owing to its critical role in the post-transcriptional regulation of inflammatory genes.[4,5] Inhibitors of p38α have been shown to block proinflammatory cytokines such as interferon-γ, TNF, IL-1β, IL-8, and cyclooxygenase-2 production from myeloid cells, in addition to reducing mortality from endotoxin-induced shock and inhibiting the development of collagen-induced arthritis in animal models.[5–7] Furthermore, activation of p38α stabilizes the 3′-untranslated region of mRNA from rapidly turned over

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Conflicts of interest

The authors disclose no conflicts.

inflammatory cytokines such as TNF and IL-1β, via adenosine-uridine–rich elements. As such, p38α seems to be critical to the regulation of proinflammatory cytokine synthesis, both at the transcriptional and translational levels.[8]

In human IBD, numerous studies have described increased p38 phosphorylation, corresponding with increased cytokine expression and leukocytic infiltration. Furthermore, in patients with ulcerative colitis and Crohn's disease, p38α expression was localized within invading macrophages and neutrophils near the intestinal epithelium.[9,10] Although a major emphasis has been placed on the role of p38α in the regulation of inflammatory cytokines, a critically important observation pertaining to IBD is that the TNF-dependent expression of mucosal address in cell adhesion molecule-1 (MAdCAM-1) is linked to p38α. MAdCAM-1 orchestrates lymphocyte homing to both Peyer's patches and gastrointestinal-associated lymphoid tissues and plays a role in the pathogenesis of IBD.[11,12]

The first synthetic p38 inhibitors, the pyridinyl imidazoles (eg, SB203580 and SB202190), showed promising anti-inflammatory results in vitro and in vivo, in models of arthritis,[13] chronic obstructive pulmonary disease, and some models of IBD.[14] Moreover, there is now a large arsenal of new p38 inhibitors (including triazanapthalenones, diaryl ureas, benzophenones, pyrazole ketones, indole amides, diamides, quinazolinones, pyrimido-pyrimidinones),[13,15] displaying efficacy in several preclinical IBD models, whereas others are currently undergoing clinical trials.[16] However, many of these studies have encountered less than satisfactory efficacy or undesired side effects. One of the limitations of current p38 inhibitors stems from their competitive inhibition of the adenosine triphosphate binding pocket, resulting in drugs with excellent potency but insufficient specificity. This lack of specificity resulted in the withdrawal of candidate molecules from clinical trials, owing to unexpected side effects such as unexplained transaminase elevation.[17] It may also explain the results of the most successful clinical trial of a p38 inhibitor in Crohn's disease (ie, CNI-1493), in which 50% of patients were in remission after 4 months, yet further analyses revealed no decreased phosphorylation of p38 in colonic biopsies. Thus, its clinical effect was attributed to JNK inhibition rather than to altered p38 activity.[10] Although attempts to improve the selectivity and pharmacodynamics of p38 inhibitors continue, this strategy remains mostly as a disappointing footnote in the search for novel IBD therapies.

Contrary to the conflicting results of broad spectrum p38 inhibitors, the cell-specific deletion of p38α has previously shown marked anti-inflammatory effects. Targeted deletion of p38α in macrophages impaired the response to the Toll-like receptor-4 ligand lipopolysaccharide (LPS) with reduced TNF, IL-12, and IL-18, in addition to reduced activation of transcription factors C/EBP-β and CREB in LPS-treated p38α-deficient macrophages. Furthermore, after in vivo challenge with LPS, p38α conditional knockout mice showed significantly lower TNF levels in sera and prolonged survival times.[18] The selective transgenic inhibition of p38α in macrophages was also protective in mice, in both acute and chronic models of cutaneous inflammation.[19] Further recent findings have elaborated on the use of cell-specific therapies in preclinical models of IBD. Delivery of anti-sense oligonucleotides targeting TNF into infiltrating colonic macrophages markedly protected mice from CD45RB^{high} and trinitrobenzene sulfonic acid–induced colitis.[20] These selective inhibition studies highlight the possibility of targeted cellular therapies for chronic inflammatory diseases, perhaps with

lessened interference with physiologic immune responses, which is a significant concern with current “biologic” therapies.

In this issue of Gastroenterology, Otsuka et al[21] have elegantly identified a dichotomy between the actions of p38 in mucosal epithelial cells and those of the infiltrating myeloid lineage, which may shed new light on the current failings of broad-spectrum p38 inhibitors in IBD (Figure 1). The authors demonstrate that, although the use of p38α/β inhibition with the antagonist SB203580 had no significant beneficial effects on clinical indices, selective deletion of p38α in myeloid cells had a protective effect in colitis induced by acute dextran sulphate sodium treatment. This protection was mediated in part by the reduced activation of the MAPK-responsive transcription factors AP-1, GAS, and NF-κB. As has been reported previously through p38 inhibition of macrophages, the expression of the colonic proinflammatory cytokines IL-1β, IL-6, IL-12p40, and TNF was reduced.[18] The authors also emphasized the critical role for p38α during physiologic epithelial cell homeostasis. Treatment of mice with the p38α/β antagonist, SB203580, and epithelial-specific p38α-deletion inhibited the homeostatic control of epithelial cell differentiation and proliferation and resulted in a decreased production of goblet cells. Because the levels of mucus secreted by goblet cells have a protective role in the intestine,[22] broad-spectrum p38α/β inhibition may predispose the intestine to epithelial damage, bacterial invasion, and dysregulated immune responses (Figure 1).

Clearly, MAPKs play important roles in transducing inflammatory signals and therefore are key molecular targets for therapeutic intervention in chronic inflammatory diseases such as IBD. However, because multiple isoforms of these kinases are implicated in the regulation of essential cellular responses, broad-spectrum MAPK inhibition is likely to result in serious side effects. By contrast, cell-specific p38α inhibition or small molecular inhibitors of the downstream, inflammation-restricted MAPK signaling of infiltrating pathogenic leukocytes during chronic inflammation is a potential novel therapeutic strategy that may further the physician’s armamentarium for the treatment of IBD in the near future.

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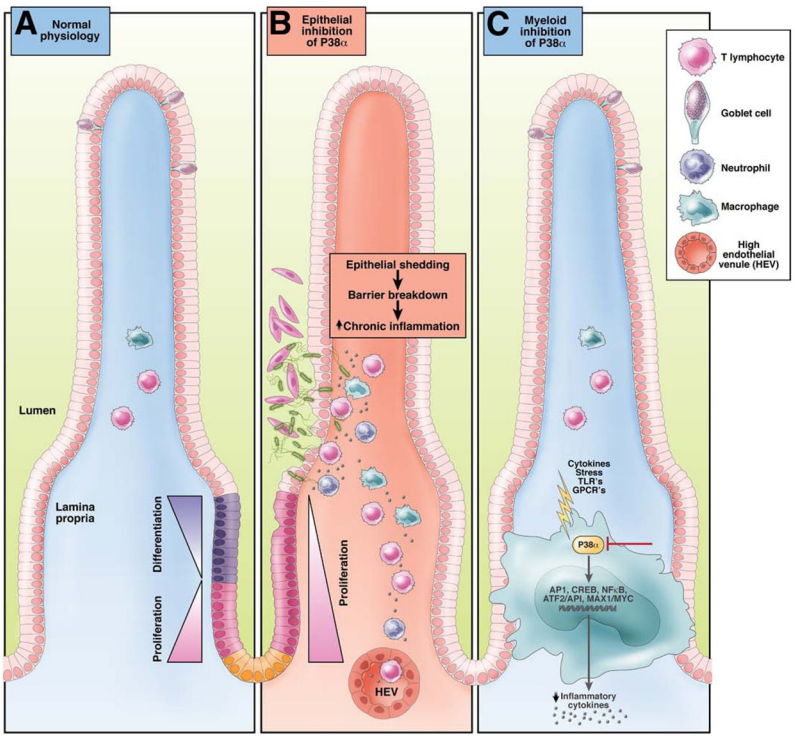

Figure 1.

Effect of selective epithelial or myeloid p38*α* inhibition on intestinal homeostasis. (*A*) Intestinal homeostasis requires the maintenance of a balance between proliferation and differentiation of epithelial precursors and the regulation of physiologic leukocyte recruitment. Mucus-secreting goblets cells have a protective role in maintaining barrier function. (*B*) Inhibition of P38*α* in epithelial cells leads to hyper proliferation and lack of goblet cell differentiation culminating in barrier breakdown and tissue injury. (*C*) Conversely, specific P38*α* inhibition in the myeloid lineage results in reduced inflammatory signaling, production of proinflammatory cytokines and marked protection from colitis.