The p38 MAPK inhibitors for the treatment of inflammatory diseases and cancer

Hae-Young Yong, Min-Soo Koh & Aree Moon

To cite this article: Hae-Young Yong, Min-Soo Koh & Aree Moon (2009) The p38 MAPK inhibitors for the treatment of inflammatory diseases and cancer, Expert Opinion on Investigational Drugs, 18:12, 1893-1905

To link to this article: http://dx.doi.org/10.1517/13543780903321490

Published online: 23 Oct 2009.

Submit your article to this journal

Article views: 822

View related articles

Citing articles: 3
The p38 MAPK inhibitors for the treatment of inflammatory diseases and cancer

Hae-Young Yong, Min-Soo Koh & Aree Moon†
Duksung Women’s University, College of Pharmacy, Seoul 132-714, Korea

Background: The p38 mitogen-activated protein kinase (MAPK) is activated by various pro-inflammatory and stressful stimuli. Mounting evidence suggests that the p38 MAPK signaling cascade is involved in various biological responses other than inflammation such as cell proliferation, differentiation, apoptosis and invasion, suggesting that the p38 MAPK can serve as a potential therapeutic target for the treatment of not only inflammatory diseases but also cancer. Methods: The unique characteristics of p38 MAPK are summarized with regard to activation and function of p38 MAPK signaling cascades. We then discuss the involvement of p38 MAPK in diseases and the implications of the possible therapeutic use of p38 MAPK inhibitors. The p38 MAPK inhibitors that have been used in the in vitro/in vivo systems as well as in the clinical trials are summarized. Results/conclusion: The p38 MAPK plays an important role in key cellular processes related to inflammation and cancer. Understanding the signal transduction mechanisms and gene regulation by p38 MAPK provides useful information in the development of p38 MAPK inhibitors with therapeutic benefits with reduced side effects. In this review, we summarize and present the list of p38 MAPK inhibitors in in vitro/in vivo studies as well as in clinical trials.

Keywords: cancer, inflammation, p38 MAPK, p38 MAPK inhibitors
2.1 Isoforms of p38 MAPK
The p38 MAPK family consists of four identified members: p38α, p38β, p38γ, and p38δ. p38α and p38β share 74% amino acid sequence homology and are ubiquitously expressed. p38γ, which has 63% amino acid sequence homology with p38α, is found predominantly in skeletal muscle. p38δ, which has 61% sequence identity with p38α, is enriched in lung, kidney, pancreas, small intestine and CD+ T cells [8,9]. Since most p38 MAPK inhibitors block the activity of both the α and β isoforms, the role of p38β in cytokine production was determined in p38β(-/-) mice. The p38β(-/-) mice showed normal lipopolysaccharide (LPS)-induced cytokine production, suggesting that p38α MAPK is the major isoform involved in the immune and inflammatory responses [10].

2.2 Activation and function of p38 MAPK signaling pathway
Since mammalian p38 MAPK was first identified during inflammation, extensive data on p38 MAPK activation have been accumulated in inflammatory responses. p38 MAPK is activated by pro-inflammatory cytokines such as interleukins and TNF-α [11,12]. The p38 MAPK pathway is also activated through stimulation of receptors including GPCR, cytokine receptors, Toll-like receptors, growth factor receptors, and receptors associated with environmental stress such as heat shock, radiation and ultraviolet light [5,13,14], demonstrating that a variety of signaling events trigger the activation of p38 MAPK pathway. It must be noted that the activation of p38 MAPK is dependent on cell type [15,16]. Selective activation of p38 MAPK isoforms by upstream kinases has been observed [17-20].

The p38 MAPK is activated by upstream MAPK kinases (MKK) [5,21]. MKK6 activates all four p38 isoforms whereas MKK3, which is 80% homologous to MKK6, activates p38δ, p38γ and p38β. Many studies have documented that MKK6 is the major activator of p38 MAPK [21-24]. MKK4 has also been shown to phosphorylate p38δ and p38β in specific cells under the direction of select stimuli [17]. MKK7 activates p38δ in 293T human kidney cells [18].

The signaling pathways upstream of the MKK/p38 pathway are diversified. Heterotrimeric guanine nucleotide-binding proteins, G proteins, can activate p38 MAPK via MKK3 and MKK6 [25]. Rac and Cdc42 have been identified as potential regulators of the p38 MAPK pathway: co-expression of constitutively active forms of Rac and Cdc42 leads to activation of p38 MAPK, while dominant-negative constructs of Rac and Cdc42 inhibit the ability of IL-1 to increase p38 MAPK activity [26,27]. Data from our laboratory have shown that p38 MAPK is strongly activated by a mutant form of H-Ras in human breast epithelial cells [26]. Not only the small G-proteins but the large G-proteins such as GPCR and regulators of G-protein signaling (RGS) proteins are also involved in the p38 MAPK signaling pathway [29,30].

Downstream substrates of p38 MAPK include the MAPKAP kinases, MK2, MK3, and p38 regulated/activated kinase (PRAK), which are selectively phosphorylated by p38 MAPK. MK2-deficient mice, but not MK3- and PRAK-deficient mice, showed a resistance to endotoxic shock and an impaired inflammatory response, as well as a significantly decreased production of cytokines such as TNFα and IL-6 [31,32]. It has been demonstrated that p38 MAPK and MK2 exist as a preformed complex, located within the nucleus [33]. MK-2 has a nuclear export signal in the carboxyl terminal domain, which is repositioned upon phosphorylation by p38 MAPK, allowing for the translocation between the nucleus and the cytoplasm [34]. A p38 MAPK inhibitor SB203580 can block the export of p38 MAPK and MK2 from the nucleus, suggesting that the phosphorylation of MK2 plays a critical role in the translocation mechanism [35]. A closely related protein kinase, MK3, was also shown to be a substrate of p38α [36]. PRAK, a stress-activated protein, can be activated by p38α and p38β [36].

2.3 Transcriptional regulation by p38 MAPK
p38 MAPK exerts its biological effects by activating several transcription factors that are involved in various cellular functions such as apoptosis, cell growth and differentiation. Upon activation of p38 MAPK, transcription factors present in the cytoplasm or nucleus become phosphorylated and activated, leading to expression of target genes resulting in a biological response. These transcription factors include activating transcription factor (ATF)-1, ATF-2, GADD153, myocyte enhancer factor (MEF)2C, CREB, C/EBP homologous protein (CHOP), p53 and NF-κB [37-41]. ATF-2, a substrate of p38 MAPK, is a possible partner of c-Jun in the activator protein (AP)-1 complex. Our recent study has demonstrated that ATF-2 mediates MMP-2 transcriptional activation induced by p38 MAPK in MCF10A human breast epithelial cells [42]. p38 MAPK can modulate transcriptional upregulation of TNF-α expression and regulate NF-κB-dependent gene expression in LPS-stimulated macrophages [43,44].

Genes that are regulated by p38 MAPK have been revealed by using dominant negative mutants of the upstream activators of p38 MAPK, MKK3 and MKK6, as well as pharmacological inhibitors of p38 MAPK. Expression of many cytokines, transcription factors, cell surface receptors and enzymes including IL-1, IL-6, IL-8, TNF-α, iNOS, COX-2, MMP-1, MMP-2, MMP-9, MMP-13, c-jun, c-fos, junB, and LDL receptor has been demonstrated to be regulated by the p38 MAPK pathway [1,42]. Further studies identifying p38 MAPK-regulated genes would be of great importance to understand the p38 MAPK signaling pathway and application of its inhibitors for therapeutic use.

3. p38 MAPK and diseases
Mounting evidence supports the importance of the p38 MAPK pathway in inflammatory diseases and cancer. The role of p38 MAPK in such diseases is reviewed, considering its inhibitors as potential therapeutic agents for their treatment.
3.1 p38 MAPK and inflammation

p38 MAPK pathway plays a central role in the expression and activity of pro-inflammatory cytokines such as TNF-α, IL-1, IL-2, IL-6, IL-7, and IL-8 in human whole blood, cultured alveolar macrophages from guinea-pig, monocytes, synovial cells, and endothelial cells [5,45]. In addition, p38 MAPK pathway plays a regulatory role in cell proliferation and differentiation in the immune system. p38 MAPK participates in GM-CSF, CSF, EPO, and CD40-induced cell proliferation and/or differentiation [46,47]. The p38 MAPK pathway regulates the expression of several MMPs involved in inflammation such as MMP-2, MMP-9, and MMP-13 [28,42,45,48]. Additionally, p38 MAPK regulates osteoclast differentiation and bone resorption through modulation of RANKL expression [49]. This review summarizes the involvement of p38 MAPK pathway in asthma, rheumatoid arthritis, systemic inflammation, inflammatory bowel disease, brain inflammation and stroke.

3.1.1 Asthma

The p38 MAPK signaling pathway is involved in the expression of inflammatory cytokines and environmental stress, and thus may contribute to asthma and autoimmune disease [50]. The p38 MAPK inhibitors have proven to be effective in numerous in vitro and in vivo models of inflammation and are also beneficial to the resolution or modulation of diseases such as asthma [8]. SB203580 has been shown to inhibit the production of TNF-α and IL-1β in the bronchoalveolar lavage (BAL) fluid of rats [51,52]. Another p38 MAPK inhibitor, SB239063, reduced neutrophil infiltration after inhaled endotoxin and the levels of IL-8, IL-6 and MMP-9 in the BAL fluid of rats [45].

3.1.2 Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that can affect many tissues and organs. It causes inflammation in the lining of the joints and/or other internal organs [53]. The p38 MAPK signaling pathway is associated with RA, and preclinical models showed the therapeutic potential of small-molecule inhibitors [54,55]. SB203580 and SB220025 were effective in a murine model of collagen-induced arthritis. These compounds prevented progression of the disease [56,57]. SB242235, another member of the pyridinyl imidazole class, inhibits TNF-α and it has protective effects on adjuvant-induced arthritis [58]. R-130823 suppressed the exacerbation of murine collagen-induced arthritis by reducing hind paw swelling [59].

3.1.3 Systemic inflammation

p38 MAPK inhibitors have been shown to reduce LPS-induced TNF-α production [56]. Similar effects were observed with another p38 MAPK inhibitor, RWJ 67657, which reduced the release of TNF-α by LPS-treated human peripheral blood mononuclear cells and TNF-α production in LPS-injected mice and rats [60].

3.1.4 Inflammatory bowel disease

Inflammatory bowel disease is a group of inflammatory conditions of the large intestine and small intestine. It has been shown that IL-23 is overexpressed in tissues taken from mouse models of inflammatory bowel disease [61]. Knocking out IL-23 significantly reduced inflammation of the bowel, in terms of cells and pro-inflammatory cytokine production [61]. The NF-κB and MAPK cascade pathways have been identified in the pathogenesis of chronic inflammatory bowel diseases. A recent study reported that SB203580 improved the clinical score, ameliorated the histological alterations, and reduced mRNA levels of pro-inflammatory cytokines in dextran sulfate sodium (DSS)-induced ulcerative colitis mice model [62]. Furthermore, Rip-like interacting caspase-like apoptosis-regulatory protein kinase (RICK), a key component of a pathway leading to NF-κB activation, is strongly activated during experimentally induced colitis and this activation is drastically inhibited by SB203580 treatment [62].

3.1.5 Brain inflammation and stroke

Brain inflammation has been implicated in the pathogenesis of neurodegeneration in common neurological diseases such as stroke and Alzheimer’s disease [63]. McDonald and colleagues [64] reported that p38 MAPK was upregulated in the brains of a transgenic mouse model of Alzheimer’s disease. A p38 MAPK inhibitor, SB239063, reduced infarct volume and neurological deficit in rats [65-67]. Transgenic mice overexpressing APP751 (a 751-amino acid isoform of β-amyloid precursor protein) have higher activity of p38 MAPK in microglia, the main immune effector cells within the brain, and increased vulnerability to brain ischemia when compared with age-matched wild-type mice [68]. When the APP751 mice were treated with a p38 MAPK inhibitor, SD282, it protected the brain from ischemic injury and abolished the difference in ischemic vulnerability [69].

3.2 p38 MAPK and cancer

Although substantial data have been accumulated on the importance of p38 MAPK in inflammation, a growing body of literature demonstrates that p38 MAPK is associated with various cellular responses related to cancer. The role of p38 MAPK in cancer is complicated: the findings are contradictory in different systems and conditions. Most responses exerted by p38 MAPK can either protect the cells from the stress/stimuli or harm the cells, depending on the cellular context and the extent of activation. This review summarizes the role of p38 MAPK in proliferation, cell invasion and apoptosis.

3.2.1 Proliferation

p38α and p38β were found to play important roles in cell differentiation and invasion of several different cancer cells such as breast cancer, squamous carcinoma cell, colon cancer, and ovarian cancer [70-73]. The p38 MAPK pathway was found to be necessary and sufficient for neuronal differentiation, and
inhibition of this pathway by SB203580 blocked neurite outgrowth in PC12 cancer cells [74]. p38α and p38β specifically induced the malignant phenotype of squamous cell carcinoma cells by regulating cell survival, proliferation and invasion, suggesting these p38 MAPK isoforms as potential therapeutic targets in squamous cell carcinomas [75]. Increased levels of phosphorylated ERKs and p38 MAPK were detected in colon cancer [72].

SB203580 significantly sensitizes growth inhibition and apoptosis induced by exisulind in colon cancer cells [76]. Inhibition of p38 MAPK by SB202190 reduced AP-1 activity and increased the sensitivity to chemotherapy in human gastric cancer cells [77]. Another inhibitor of p38 MAPK, BIRB-796, also inhibited IL-6 secretion induced in bone marrow-derived mesenchymal stem cells, thereby inhibiting paracrine tumor cell proliferation [78].

3.2.2 Cancer invasion

Mounting evidences show the involvement of p38 MAPK in cancer cell invasion. The p38 MAPK pathway has been shown to regulate the expression of the MMP family [42,45,79], which is significantly involved in tumor invasion and metastasis formation in various cell systems [80,81]. It has been demonstrated that prostate cancer cell invasion is mediated through the p38 MAPK pathway; this leads to the phosphorylation of heat shock protein 27, which in turn regulates MMP-2 activation and cell invasion [82]. The activation of MMP-2 and the invasiveness have been shown to be mediated through p38 MAPK, but not ERK, signaling in human melanoma cells [83].

In metastatic serous ovarian carcinoma, MMP-2 activity is correlated with p38 MAPK activity [73]. Activation of p38 MAPK pathway plays a crucial role in the invasive phenotype of transformed squamous epithelial cells [84]. A recent study indicated that the p38 MAPK pathway might enhance breast cancer progression by upregulating uPA expression, and might be an important route in invasion and metastasis of breast cancer [85]. The p38 MAPK pathway stimulated MMP-9 expression/secrection and in vitro invasion of human squamous carcinoma cell lines [71]. In ovarian cancer cells, the p38 MAPK signaling pathway is required for the induction of MMP-9 [86]. The p38 MAPK activation is critical for induction of the expression of invasion-associated MMPs such as MMP-13, MMP-1 and MMP-9 in transformed keratinocytes [87].

Involvement of the p38 MAPK pathway in breast cell invasion was demonstrated by several laboratories, including ours. p38 MAPK is activated in invasive H-Ras MCF10A human breast epithelial cells, but not in noninvasive N-Ras MCF10A cells [28]. We further showed that H-Ras-specific activation of the Rac/MKK-6/p38 MAPK signaling pathway upregulated MMP-2, leading to invasion and migration of MCF10A cells [79]. The p38 MAPK pathway activates ATF-2, which then results in transcriptional activation of MMP-2 through binding to the functional AP-1 site [42]. Phosphorylation of heat shock protein 27 by p38 MAPK has been shown to induce the migration of MDA-MB-231 breast cancer cells on a laminin-5-coated dish [70]. It was also suggested that p38 MAPK might be critical in heregulin-β1-mediated MMP-9 induction in breast cancer cells [88].

3.2.3 Apoptosis

Stress-activated protein kinases, including c-Jun N-terminal kinase and p38 MAPK, seem to counteract malignant transformation. Many studies suggest that p38 MAPK can also function as a tumor suppressor. p38 MAPK is associated with apoptosis in some cell systems. It has been reported that p38 MAPK activates p53 and p53-induced apoptosis. p38 MAPK binds to p53 to form a complex, leading to phosphorylation of p53, thereby enhancing its functional activities [89]. SB202190 and dominant-negative p38 MAPK blocked the induction of p53-mediated induction of apoptosis in an epithelial cell line [90,91]. p38 MAPK activity has been shown to induce apoptosis in hepatocellular carcinoma cell lines [92]. p38 MAPK acts as a negative regulator of cell cycle progression. Inhibition of p38 MAPK decreased the G1-S phase progression in FRTL-5 thyroid cells [93]. An in vivo xenograft study showed that induction of apoptosis was associated with activation of p38 MAPK and JNK1/2 in protoapigenone-treated prostate tumor tissues [94]. p38 MAPK plays a major role in anisomycin-reduced macrophage content of rabbit atherosclerotic plaques through apoptosis; a p38 MAPK inhibitor, SB202190, prevented macrophage cell death [95]. p38 MAPK has been shown to induce apoptosis in some cells, but plays an anti-apoptotic role in a number of other cell types [96,97]. Similarly, opposed effects of p38 MAPK have been observed with respect to cell cycle regulation [91]. Talmapi mod (SCIO-469) enhanced bortezomib-induced apoptosis of multiple myeloma by the increase in the level of p53 or the reduction of Bel-1XL levels in vitro. Animals treated with talmapi mod and/or bortezomib showed a significant inhibition in tumor weight of multiple myeloma [98].

4. p38 MAPK inhibitors

4.1 Mode of inhibition

p38 inhibitors can be divided into two groups depending on their mode of binding to p38 MAPK: i) active site inhibitors, such as SB203580, which bind competitively to the ATP site of the enzyme; and ii) others, including BIRB-796, which bind remotely and interfere with ATP binding indirectly. SB203580 is reported to be the first selective inhibitor of p38α and p38β isoforms [99], but is not effective for p38γ and p38δ [100]. SB203580 binds to the active site of p38 MAPK in an ATP-competitive manner. This type of inhibitor binds directly to an argyl-specific pocket behind the site, which is normally occupied by the adenine ring of ATP. The urea-containing p38α inhibitors such as BIRB-796 bind to the site remote from the ATP pocket, and prevent ATP binding [101]. p38 MAPK inhibitors including SB203580, AMG548, BIRB 796, and pamapimod (RO4402257) show kinase selectivity profiling (Table 1). SB203580 has a good selectivity...
for p38α and p38β over the majority of kinases, but does inhibit some MAPKs, such as JNK3 [102,103]. AMG548 is exquisitely potent for p38α, slightly selective against p38β, and > 1000-fold selective against p38γ and p38δ [104]. BIRB 796 has sub-nM potency against p38α and is selective against JNK2 [105]. Pamapimod preferentially inhibits the α and β isoforms without activity against the γ or δ isoforms [106].

Table 1. Selectivity profiles for p38 MAPK inhibitors.

<table>
<thead>
<tr>
<th>Kinases</th>
<th>SB203580*</th>
<th>AMG548‡</th>
<th>BIRB796*</th>
<th>Pamapimod§</th>
</tr>
</thead>
<tbody>
<tr>
<td>p38α</td>
<td>17</td>
<td>0.5</td>
<td>2</td>
<td>1.3</td>
</tr>
<tr>
<td>p38β</td>
<td>250</td>
<td>3.6</td>
<td>220</td>
<td>120</td>
</tr>
<tr>
<td>p38γ</td>
<td>1700</td>
<td>2591</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td>p38δ</td>
<td>-</td>
<td>4100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>JNK1</td>
<td>1200</td>
<td>11,400</td>
<td>Inactive</td>
<td>190</td>
</tr>
<tr>
<td>JNK2</td>
<td>95</td>
<td>39</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>JNK3</td>
<td>45</td>
<td>61</td>
<td>62</td>
<td>19</td>
</tr>
</tbody>
</table>

*Kd values from Ambit; Inactive is from a 10 uM primary screen.
‡Data from Amgen’s internal discovery programs; potencies provided for p38 α, p38β, p38γ, JNK1, JNK2 and JNK3 are IC50 values.
§Kd values were determined for all kinases that demonstrated > 85% inhibition [106].

4.2 p38 MAPK inhibitors for in vitro and in vivo studies

Table 2 is a list of the p38 MAPK inhibitors that have been demonstrated to prevent diseases in vitro and in vivo. This review summarizes p38 MAPK inhibitors used for inflammatory diseases and cancer.

4.2.1 p38 MAPK inhibitors for inflammatory diseases

SB203580 inhibited production of pro-inflammatory cytokines such as TNF-α and IL-1β in inflammatory disease models [51,52,62]. SB239063 reduced pro-inflammatory cytokines including IL-8, IL-6 and MMP-9 in a rat asthma model [45]. It also reduced infarct volume in a rat model of brain inflammation [65-67]. SB242235 and RWJ67657 inhibited TNF-α release in RA and systemic inflammation models [58,60]. SB220025 was able to prevent RA progression in the collagen-induced murine model [57].

4.2.2 p38 MAPK inhibitors for cancer-related diseases

SB203580 significantly reduced neuronal outgrowth and induced the apoptosis in cancer cells [74,76]. Data from our laboratory demonstrate the inhibitory effect of SB203580 on invasive and migratory phenotypes induced by actively mutated H-Ras [28,42] and by TGF-β [107-109] in MCF10A human breast epithelial cells. SB203580 also inhibited the glial cell-derived neurotrophic factor-induced human glioma cell migration [110]. BIRB-796 inhibited progression of cancer cells by suppression of IL-6 production and proliferation [78]. A recent report indicated that SB202190 can reduce AP-1 activity and increase the sensitivity of chemotherapy in gastric cancer cells [77].

4.3 p38 MAPK inhibitors in clinical trials

p38 MAPK inhibitors have been evaluated preclinically in a wide range of disease models with a considerable efficacy. Although many pharmaceutical companies have ongoing clinical trials for p38 MAPK inhibitors, some of this work has failed due to safety issues. Table 3 summarizes the list of p38 MAPK inhibitors that have been progressed in clinical trials. We also describe concerns about potential side effects related to the treatment with p38 MAPK inhibitors.

4.3.1 AMG-548 (Amgen)

AMG-548 was the first internal small-molecule clinical candidate for Amgen. Based on the overall profile of AMG-548, the compound proceeded to Phase I clinical trials. Inhibition of ex vivo whole blood LPS-induced cytokine production was observed at oral doses of 3, 10, 30, 60, 100 and 300 mg/day [111]. A single oral dose of 300 mg AMG-548 can inhibit 80 – 95% of cytokines such as TNF-α and IL-1β. These data demonstrate that AMG-548 is a potent p38 inhibitor with suitable pharmacokinetics for once-daily oral dosing. However, the drug was associated with side effects such as elevations of liver enzyme [112]. It was reported that elevations of isolated liver enzyme were observed in 9 out of 54 people (16.7%) randomized to AMG-548, and 1 out of 18 (6%) randomized to placebo [111].

4.3.2 BIRB-796/BIRB-796BS (Boehringer Ingelheim)

BIRB-796 is a small-molecule inhibitor of p38 MAPK and a potential agent for the treatment of inflammatory diseases. BIRB-796 inhibited TNF-α when challenged with LPS in a dose-dependent manner [113]. It exerted comparable inhibition of TNF-α production [114]. A 600-mg dose of BIRB-796BS significantly inhibited LPS-induced coagulation, fibrinolysis and endothelial cell activation in a dose-dependent manner during human endotoxemia [115]. In Phase I randomized, placebo-controlled, double-blind clinical studies with a single escalating dose (1 – 600 mg) and 7-day multi-dose (20, 50 and 150 mg), BIRB-796 showed a symptomatic dose-related rise in alanine transaminase (ALT) or aspartate transaminase (AST) levels [105]. BIRB-796 was tested in an 8-week study of 284 persons with moderate to severe Crohn’s disease, but failed to show any clinical benefit [116].

4.3.3 Pamapimod (Roche)

A pyridopyrimidine class pamapimod (RO4402257) is a novel inhibitor of p38. In the in vitro and in vivo preclinical studies, pamapimod reduced production of inflammatory cytokines such as TNF-α, IL-1β and IL-6 [107]. However, in a 12-week study with 50, 150, and 300 mg once-daily doses, pamapimod demonstrated lower frequencies of response according to the American College of Rheumatology 20 improvement criteria (ACR20) and the Disease Activity Score in 28 Joints (DAS28), compared with the group taking methotrexate [117]. In pamapimod-treated patients with active
The p38 MAPK inhibitors for the treatment of inflammatory diseases and cancer

4.3.4 RWJ-67657 (Johnson & Johnson)

RWJ-67657 was reported to reduce TNF-α, IL-6 and IL-8 (which have been associated with the development of flu-like symptoms [119]) in a dose-dependent manner [120]. Effects of the RWJ-67657 were demonstrated in a study that included 62 healthy volunteers randomized to receive either placebo or a single oral dose of RWJ-67657 (350, 700 or 1400 mg/kg). Both the symptoms and the cytokine levels were decreased dose-dependently, suggesting the utility of RWJ-67657 in the treatment of sepsis and cytokine-mediated diseases [121]. However, development of this compound was discontinued due to low bioavailability [122].

4.3.5 SB-681323/Iosmapimod (856553) (GlaxoSmithKline)

Currently underway is a double-blind, placebo-controlled study of orally administered SB-681323 (7.5 mg, b.i.d.) in individuals with neuropathic pain following nerve trauma [123].

### Table 2. p38 MAPK inhibitors in *in vitro* and *in vivo* studies.

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Indication</th>
<th>Model</th>
<th>Outcome</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SB203580</td>
<td>Asthma</td>
<td><em>In vivo</em>: in BAL fluid of rat</td>
<td>Inhibition of TNF-α and IL-1β production</td>
<td>[51,52]</td>
</tr>
<tr>
<td></td>
<td>RA</td>
<td><em>In vivo</em>: Murine model of collagen-induced arthritis</td>
<td>Prevention of RA progression</td>
<td>[56]</td>
</tr>
<tr>
<td></td>
<td>Inflammatory bowel disease</td>
<td><em>In vivo</em>: DSS-induced ulcerative colitis mice model</td>
<td>Reduction of mRNA levels of pro-inflammatory cytokines; RICK inhibition</td>
<td>[62]</td>
</tr>
<tr>
<td></td>
<td>Cancer-related diseases</td>
<td><em>In vitro</em>: PC12 cancer cells</td>
<td>Block of neuronal outgrowth</td>
<td>[74]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>In vitro</em>: Colon cancer cells</td>
<td>Growth inhibition and apoptosis induction</td>
<td>[76]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>In vitro</em>: Human breast epithelial cells</td>
<td>Inhibition of H-Ras-induced invasion/migration</td>
<td>[28,42]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>In vitro</em>: Human breast epithelial cells</td>
<td>Inhibition of TGF-β-induced invasion/migration</td>
<td>[107-109]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>In vitro</em>: Human glioma cells</td>
<td>Inhibition of GDNF-induced migration</td>
<td>[110]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>In vivo</em>: in BAL fluid of rat</td>
<td>Reduction of neutrophil infiltration, IL-8, IL-6 and MMP-9</td>
<td>[45]</td>
</tr>
<tr>
<td>SB239063</td>
<td>Asthma</td>
<td><em>In vivo</em>: in rat</td>
<td>Reduction of infarct volume</td>
<td>[65-67]</td>
</tr>
<tr>
<td></td>
<td>Brain inflammation and stroke</td>
<td><em>In vivo</em>: Murine model of collagen-induced arthritis</td>
<td>Prevention of RA progression</td>
<td>[57]</td>
</tr>
<tr>
<td>SB220025</td>
<td>RA</td>
<td><em>In vivo</em>: Murine model of collagen-induced arthritis</td>
<td>Prevention of RA progression</td>
<td>[57]</td>
</tr>
<tr>
<td>SB202190</td>
<td>Cancer</td>
<td><em>In vitro</em>: Human gastric cancer cells</td>
<td>Reduction of AP-1 activity; Increase of the sensitivity of chemotherapy</td>
<td>[77]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>In vitro</em>: Human glioma cells</td>
<td>Inhibition of GDNF-induced migration</td>
<td>[110]</td>
</tr>
<tr>
<td></td>
<td>Atherosclerosis</td>
<td><em>In vivo</em>: in rabbit</td>
<td>Prevention of RA progression</td>
<td>[57]</td>
</tr>
<tr>
<td>SB242235</td>
<td>RA</td>
<td><em>In vivo</em>: Murine model of adjuvant-induced arthritis</td>
<td>Inhibition of TNF-α</td>
<td>[58]</td>
</tr>
<tr>
<td>RWJ67657</td>
<td>Systemic inflammation</td>
<td><em>In vivo</em>: LPS-injected mice and rats</td>
<td>Reduction of TNF-α release</td>
<td>[60]</td>
</tr>
<tr>
<td>SD282</td>
<td>Brain inflammation and stroke</td>
<td><em>In vivo</em>: APP571 mice (have higher activity of p38 MAPK)</td>
<td>Protection of brain against ischemic injury</td>
<td>[69]</td>
</tr>
<tr>
<td>BIRB-796</td>
<td>Cancer</td>
<td><em>In vitro</em>: Paracrine tumor cell</td>
<td>Inhibition of IL-6 secretion and proliferation</td>
<td>[78]</td>
</tr>
<tr>
<td>R-130823</td>
<td>RA</td>
<td><em>In vivo</em>: Murine model of adjuvant-induced arthritis</td>
<td>Reduction of hind paw swelling</td>
<td>[59]</td>
</tr>
<tr>
<td>Talmapiomod (SCIO-469)</td>
<td>MM</td>
<td><em>In vivo</em>: Mouse plasmacytoma model of MM</td>
<td>Inhibition of MM tumor weight</td>
<td>[98]</td>
</tr>
</tbody>
</table>

BAL: Bronchoalveolar lavage; DSS: Dextran sulfate sodium; GDNF: Glial cell-derived neurotrophic factor; LPS: Lipopolysaccharide; MM: Multiple myeloma; RA: Rheumatoid arthritis; RICK: Rip-like interacting caspase-like apoptosis-regulatory protein kinase.
A 28-day randomized, double-blind, placebo-controlled study in individuals with coronary heart disease undergoing percutaneous coronary intervention is also currently underway [5].

A novel p38 kinase inhibitor, ioxopimod (856553) is in Phase II clinical trials for cardiovascular disease, chronic obstructive pulmonary disease and depression [124].

### 4.3.6 Talmapimod (SCIO-469)/SCIO-323 (Scios)

Talmapimod (SCIO-469) has been tested in a 12-week RA study, where it elicited an ACR20 response in 53% of persons compared with 23% for placebo [5]. In addition, SCIO-323, the back-up candidate to talmapimod, was reported to be a selective inhibitor for p38α with an improved efficacy in an autoimmune model of RA [111]. SCIO-323 has advanced into a Phase I clinical trial [125]. Talmapimod has been studied compared with ibuprofen, with the time to rescue pain medication as the efficacy end point in a dental model. In the study of 263 people, 150 or 300 mg of talmapimod extended the time to decrease pain medication from 4.1 h in placebo to 6.1 and 5.7 h in the low and high doses, respectively [126]. The most significant response (8.1 h) was accomplished by the administration of 210 mg prior to and another 90 mg at the time of surgery, suggesting an analgesic effect of the compound [5].Moreover, talmapimod is recently undergoing a Phase II clinical trial for multiple myeloma and myelodysplastic syndromes [124]. Recently, talmapimod has been in Phase II clinical trials for active RA. It was reported that ACR20 response rates between each talmapimod-treated group versus placebo at week 12 did not reach statistical significance. In addition, trends in improvement were observed at week 2, especially in CRP, but did not persist to week 12 [127].

### 4.3.7 VX-745/VX-702 (Vertex)

VX-745 was reported to inhibit production of LPS-induced TNF-α in whole blood [128]. Lower doses of the compound were well tolerated and produced a significant clinical benefit. VX-745 has been in Phase II clinical trials for RA and reported to achieve an ACR20 response in 43% of the treated group compared with 17% for placebo. In addition, there was a dose-dependent inhibition of inflammatory biomarkers such as CRP and IL-6 [129]. However, VX-745 can cross the blood–brain barrier and exert adverse neurological side effects and elevation in liver transaminases in preclinical studies [129,130].

VX-702 was evaluated in patients with acute coronary syndrome undergoing percutaneous coronary intervention.
Vertex Pharmaceuticals, Inc. reported that VX-702 can strongly reduce CRP levels in serum of patients undergoing percutaneous coronary intervention, and the CRP levels remained significantly lowered up to 4 weeks beyond the 5-day dosing period [134]. A 12-week, double-blind, randomized, placebo-controlled Phase II study in patients with RA was conducted, and demonstrated only modest ACR20 response compared with substantial placebo effects. Inflammatory biomarkers including CRP, soluble TNF receptor p55 and serum amyloid A showed an initial reduction; however, after week 2 they began to return to baseline and remained there until week 12. Taken together, the clinical studies on VX-702 have shown modest clinical efficacy plus the transient suppression of biomarkers of inflammation [132,133].

4.4 Feedback regulation on p38 MAPK and functional consequences of p38 MAPK inhibition

p38α leads to feedback control loops that suppress the activities of upstream MAP kinase kinase kinases (MAP3Ks), such as TAK1 [134] and MLKs [135], which are associated with activation of other pro-inflammatory pathways, including those that lead to the activation of JNK. p38α inhibitors abolish these feedback control loops, leading to the hyper-activation of TAK1, MLKs and JNK, which may contribute to liver problems [134]. Several groups have reported that p38 MAPK inhibition induced activation of JNK in many human cell types [135-137]. However, livers of p38α-deficient mice were not sensitive to LPS/TNF challenge despite increased JNK activation [136]. p38α collaborates with IkB kinase to protect hepatocytes from TNF-induced death by controlling JNK activation [136].

Recent studies reported that inactivation of p38 MAPK increased tumorigenesis. Loss of p38 MAPK activation in MKK3/MKK6-knockout animals was associated with defects in growth arrest and increased tumorigenic potential [138]. The downregulation of p38α in adult mice leads to an immature and hyperproliferative lung epithelium that is highly sensitized to tumorigenesis induced by the K-ras G12V [139,140]. p38α can activate anti-inflammatory cytokines as well as the pro-inflammatory cytokines [141-143], and its inhibitors may suppress both anti-inflammatory and pro-inflammatory effects. p38α activates mitogen and stress-activated kinase 1 (MSK1) and MSK2, which prevent the production of pro-inflammatory cytokines and thus limit inflammatory responses [142,144]. Some of the p38 MAPK inhibitors may eventually be found useful as anti-inflammatory drugs in situations where local application might be possible and/or where the treatment period is relatively short [144,145].

5. Conclusions

The p38 MAPK plays an important role in key cellular processes related to inflammation and cancer. This review summarizes the properties of the p38 MAPK pathway with regard to its activation and function. We discuss the unique characteristics of p38 MAPK and highlight its involvement in inflammatory diseases and cancer with the implications of the possible therapeutic use of p38 MAPK inhibitors. The p38 MAPK inhibitors, which have been used in the in vitro/in vivo systems as well as in the clinical trials, are examined and their therapeutic potential summarized.

6. Expert opinion

A substantial body of data on the importance of p38 MAPK signaling in inflammatory responses has been accumulated, suggesting that p38 MAPK can serve as a potential therapeutic target for the treatment of inflammatory diseases. Understanding the signal transduction mechanisms and gene regulation by p38 MAPK would provide useful information in the development of p38 MAPK inhibitors with therapeutic benefits that have reduced side effects.

Although hundreds of studies on p38 MAPK inhibitors and a handful of compounds have been reported, no drug has yet been developed for clinical use. This may be because the right dose regimen or indication has yet to be identified. There are concerns about the adverse side effects due to toxicity involved in inhibition of this target. Low bioavailability can also be an obstacle to clinical use. The poor clinical efficacy of p38 MAPK inhibitors may be due to the fact that p38α exerts dual effects on inflammation: it can activate anti-inflammatory cytokines as well as the pro-inflammatory cytokines, and thus its inhibitors may suppress or activate inflammatory responses. Moreover, since p38 MAPK plays multiple roles in physiological systems other than inflammation, suppression of this kinase may cause many of the adverse problems unrelated to inflammation. Additional studies are necessary to elucidate the complex role of p38 MAPK for the potential development of p38 MAPK inhibitors as anti-inflammatory drugs.

The role of p38 MAPK in cancer is complicated and the findings are somewhat contradictory, depending on different systems and conditions. A growing number of studies, however, suggest the possible application of p38 MAPK inhibitors in the treatment of diseases related to cancer. Based on the evidences showing the in vitro effect of p38 MAPK inhibitors on cancer cell proliferation, invasion and migration, further in vivo and clinical studies would provide more information regarding the potential application of p38 MAPK inhibitors for therapeutic use for cancer.

Acknowledgements

This work was supported by the KOSEF NRL Program (MEST, No. ROA-2008-000-20070-0), and by the KOSEF (MEST, No.R11-2007-107-01002-0).

Declaration of interest

The authors declare no conflicts of interest and have received no payment for the preparation of this manuscript.


20. Enslen H, Raingeaud J, Davis RJ. Selective activation of p38 mitogen-activated protein (MAP) kinase isoforms by the stress-activated protein kinase-3 (SAPK3) by cytokines and cellular stresses is mediated via SAPK3K (MKK6); comparison of the specificities of SAPK3 and SAPK2 (RK/p38). EMBO J 1997;16:295-305


The p38 MAPK inhibitors for the treatment of inflammatory diseases and cancer


64. McDonald DR, Bamberger ME, Combs CK, Landreth GE. Beta-amyloid fibrils activate parallel mitogen-activated protein kinase pathways in microglia and THP1 monocytes. J Neurosci 1998;18:4451-60


67. Barone FC, Irving EA, Ray AM, et al. Inhibition of p38 mitogen-activated protein kinase provides neuroprotection in


82. Xu L, Chen S, Bergan RC. MAPKAPK2 and HSP27 are downstream effectors of p38 MAP kinase-mediated matrix metalloproteinase type 2 activation and cell invasion in human prostate cancer. Oncogene 2006;25:2987-98


89. She QB, Chen N, Dong Z. ERKs and p38 kinase. Cancer Res 2003;63:5278-84


98. Navas TA, Nguyen AN, Hideshima T, et al. Inhibition of p38alpha MAPK enhances proteasome inhibitor-induced apoptosis of myeloma cells by modulating
The p38 MAPK inhibitors for the treatment of inflammatory diseases and cancer

Hsp27, Bel-X(L), Mcl-1 and p53 levels in vitro and inhibits tumor growth in vivo. Leukemia 2006;20:1017-27


111. Dominguez C, Powers DA, Tamayo N. p38 MAP kinase inhibitors: many are made, but few are chosen. Curr Opin Drug Discov Devel 2005;8:421-30


128. Song H, Moon A. Glial cell-derived neurotrophic factor (GDNF) promotes low-grade H683 glioma cell migration through JNK, ERK-1/2 and p38 MAPK signaling pathways. Neurosci Res 2006;56:29-38


130. Vertex Pharmaceuticals Inc. Vertex moves to re-allocate resources from VX-745 in p38MAP kinase program to accelerate development of second generation drug candidates VX-702 and VX-850. Press Release 2001

131. Vertex Pharmaceuticals Inc. Preliminary Phase IIa data for VX-702 demonstrate tolerability and reduction in C-reactive protein in cardiovascular patients. Rome: European Society of Cardiology’s Acute Cardiac Care Symposium, 17-20 October 2004


Affiliation
Hae-Young Yong, Min-Soo Koh & Aree Moon†
†Author for correspondence
Duksung Women’s University, College of Pharmacy, Seoul 132-714, Korea
Tel: +82 2 901 8394; Fax: +82 2 901 8386;
E-mail: armoon@duksung.ac.kr