Mitogen activated protein (MAP) kinase signal transduction pathways and novel anti-inflammatory targets

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Over the last decade important advances have been made in our understanding of the molecular events underlying cellular responses to extracellular signals. Increased understanding of signal transduction mechanisms and gene regulation involved in immune responses has created opportunities for the discovery of novel therapeutic compounds useful in treating inflammatory disorders. One of the best studied signalling routes is the mitogen activated protein (MAP) kinase signal transduction pathway which plays a crucial role in many aspects of immune mediated inflammatory responses. Here, our current understanding of the MAP kinase pathway is reviewed, as well as recent advances in the design of novel agents that are able to modulate the activity of these signalling cascades.

SUMMARY

Proper regulation of genes in all forms of cellular life is dependent on intracellular regulatory circuits or signal transduction pathways. Among eukaryotic cells, phosphorylation of intracellular factors followed by specific gene transcription is a universal outcome of such signal transduction pathways, and the major elements of such pathways are similar in species as different as humans, fungi, and plants. In mammalian species, these ancient regulatory circuits maintain the balanced gene transcription necessary for correct cell growth, differentiation, and death. Scientific interest in these information highways from the cell surface to the nucleus has exploded over the past years, and understanding of the biology of these signalling cascades has progressed dramatically. One of the best studied signalling routes is the mitogen activated protein (MAP) kinase signal transduction pathway which plays a crucial role in many aspects of immune mediated inflammatory responses. Hence members of this family of kinases have come to be appreciated as key cellular signal transducers and attractive targets for drug development. This has led to current initiation of clinical trials in inflammatory disease states evaluating small molecule inhibitors of MAP kinase proteins and encouraging results have been obtained. Because it is anticipated that several small MAP kinase inhibiting molecules will be evaluated for efficacy in inflammatory diseases, here we review current knowledge of the MAP kinase signalling pathways as well as potential inhibitory drugs.

INTRODUCTION

During the last decade important advances have been made in our understanding of the molecular events underlying cellular responses to extracellular signals. This scientific progress has set the stage for an exciting new field of research: pharmacological modulation of signal transduction pathways to control gene expression. Altered gene expression plays a key role in the pathogenesis of many inflammatory diseases such as pancreatitis, rheumatoid arthritis, hepatitis, psoriasis, and inflammatory bowel disease. It is only in recent years that signal transduction mechanisms responsible for inducing inflammatory gene expression have been identified. These mechanisms seem fundamental in the initiation of inflammatory responses. Products of induced inflammatory genes include cytokines, chemokines, and adhesion molecules that serve to promote recruitment of immunocompetent cells from the circulation to the affected site which results in an inflammatory injury. It is for this reason that these intracellular pathways have come to be appreciated as attractive targets for drug development.

The aim of this review is to present the current understanding of the MAP kinase pathway, a key mechanism of inflammatory signal transduction in eukaryotic cells. Furthermore, we will review recent advances in the design of novel agents that are able to modulate the activity of these signalling cascades.

SIGNAL TRANSDUCTION AND CONTROL OF GENE EXPRESSION.

There are two major routes from extracellular signalling proteins to changes in gene transcription (fig 1). Firstly, several intracellular self propagating phosphorylation cascades have been identified that activate different resident nuclear transcription factors. Secondly, a number of latent cytoplasmic transcription factors are activated after cell surface receptor-ligand interactions that

**Abbreviations:** AP-1, activating protein 1; ATF-2, activating transcription factor 2; ERK, extracellular signal regulated kinase; IFN, interferon; IL, interleukin; JAK, Janus kinase; JNK, c-Jun NH2 terminal kinase; LPS, lipopolysaccharide; MAP, mitogen activated protein; MAPK, MAP kinase; MAPKAP, MAP kinase activated protein kinase; MAPKK, MAP kinase kinase; MAPKKK, MAP kinase kinase kinase; MEK, MAP/ERK kinase; MEF, myocyte enhance factor; NGF, neurotrophic factor; NF, nuclear factor; STAT, signal transducers and activators of transcription; TGF, transforming growth factor; TNF, tumour necrosis factor.
accumulate in the nucleus to drive transcription. Recently, a classification system for transcription factors was proposed to structure this still increasing repertoire of intracellular proteins regulating cell development and cell specialisation.

MAP kinases, which belong to a large family of serine/threonine kinases, constitute major inflammatory signalling highways from the cell surface to the nucleus. Other kinase cascades include those that are activated after increases in intracellular second messengers (including cAMP and Ca$^{2+}$) and ligand interaction with G coupled cell surface receptor proteins and receptor tyrosine kinases. Usually such pathways result in the phosphorylation and subsequent activation of transcription factors, producing altered gene transcription.

Eight principal pathways for activation of latent cytoplasmic transcription factors are now recognised. The two pathways that are directly activated at the cell surface receptor are the family of SMAD molecules that are involved in signal transduction of the transforming growth factor β (TGF-β) superfamily of ligands, and the STAT family (signal transducers and activators of transcription) which are activated by more than 20 cytokines sharing Janus kinase (JAK) associated receptors that phosphorylate the respective receptors on tyrosine residues to initiate signal transduction. In short, inactive JAK enzymes are loosely attached to the cytoplasmic domains of specific cytokine receptors (including interferon (IFN)-α/β/γ, interleukin (IL)-2, IL-4, IL-6, IL-10, and IL-12). After ligand binding, the receptor associated JAKs become active through phosphorylation, and in their turn phosphorylate tyrosine residues in the cytoplasmic portions of the clustered receptors. Subsequently, cytosolic STAT proteins recognise these phosphoryrosine moieties and are phosphorylated after attachment to the receptors by receptor associated JAKs. After binding of two STAT proteins, they dissociate from the receptor and migrate to the nucleus where they bind to DNA sequences in the promoter regions of cytokine responsive genes and activate gene transcription. STAT activation may have important consequences. For instance, in T helper cell differentiation, STAT4 activation is sufficient to confer a T helper 1 cell phenotype whereas STAT6 activation causes transition from a precursor cell to a T helper 2 cell.

"The Wnt signalling pathway is pivotal in normal and malignant development"

Four other important pathways that can activate latent transcription factors require cytoplasmic serine phosphorylation and/or proteolysis. This group includes the Rel/nuclear factor κB (NFκB) family which is activated by, and essential for, correct response to a wide variety of extracellular stimuli such as tumour necrosis factor α (TNF-α), IL-1, and viral and bacterial products. This group also includes the Wnt pathway and the Notch pathway. The Wnt signalling pathway is pivotal in normal and malignant development. For example, adenomatous polyposis coli protein has been thought to function as a tumour suppressor through its involvement in the Wnt/β-catenin signalling pathway. The Notch signalling pathway has been implicated in lymphopoiesis: recent data suggest that Notch activity plays a pivotal role in T cell lineage commitment from the common lymphoid progenitor. Furthermore, Notch signalling seems crucial in the developing nervous system; its function determines cell fate from the first segregation of neuronal precursors to the terminal specification of cells as neurones and glia.

Finally, fluctuations in cytoplasmic second messengers (Ca$^{2+}$ and phosphoinositide concentrations) can activate latent cytoplasmic transcription factors such as nuclear factors in activated T cells (NFAT) and Tubby, a product of a gene which is associated with obesity. A detailed analysis of the aforementioned signalling mechanisms lies beyond the aim of this review, and we will focus on the most ancient and conserved signalling pathway that is pivotal during immune responses: the MAP kinase pathway.

**MAP KINASE PATHWAY**

MAP kinases are an evolutionarily conserved family of enzymes that form a highly integrated network required to achieve specialised cell functions controlling cell differentiation, cell proliferation, and cell death. These cytoplasmic proteins can modulate the activities of other intracellular proteins by adding phosphate groups to their serine/threonine amino acids (fig 2). To date, over 20 MAP kinase isoforms have been reported, which are summarised in table 1. Activation of MAP kinase enzymes themselves is unusual in that they require phosphorylation on both a threonine (Thr) and tyrosine (Tyr) residue and thus need the activity of dual specificity kinases which are known as MAP/ERK kinases (MEKs) or MAP

**Figure 1** Different routes from extracellular signalling proteins to changes in gene transcription. Left: Intracellular phosphorylation cascades activate nuclear transcription factors. Right: Latent cytoplasmic transcription factors are activated on receptor-ligand interaction.
kinase kinases (the phosphorylating potential of all other mammalian kinase families is restricted to either phosphorylation of serine/threonine residues or tyrosine residues). The specificity of MEK for MAP kinase is context dependent: all MEK enzymes exert their dual phosphorylation on Thr-Xxx-Tyr amino acid sequence motifs but the X confers specificity. The amino acid X is glutamic acid (Glu) for extracellular regulated protein kinase (ERK), proline (Pro) for c-Jun NH2 terminal kinase (JNK), and glycine (Gly) for p38 MAP kinase. ERK MAP kinases are activated by MAP kinase kinase (MKK) 1 and MKK2, JNK by MKK4 and MKK7, and p38 MAP kinase by MKK3, MKK4, and MKK6 (fig 3). Hence activation of a specific MEK will result in a defined set of further cellular consequences.

The activity of MEKs is in turn controlled by phosphorylation, phosphorylated MEKs being enzymatically active. This phosphorylation status is under the critical control of so-called MAP kinase kinase kinases (MAPKKK, M KK, or MEKK), a family of proteins of which the c-Raf proto-oncogene is the most prominent member. The control of this family of enzymes and their substrate specificity is still only partially understood.

On activation of MAP kinases, transcription factors present in the cytoplasm or nucleus are phosphorylated and activated, leading to expression of certain target genes resulting in a biological response. The multiple interactions between the different MAP kinase cascades serve to integrate responses and to moderate outputs. Indeed, it has been demonstrated that MAP kinases have overlapping substrate specificities and phosphorylation of regulatory sites is shared among multiple protein kinases.

As noted above, three major groups of distinctly regulated groups of MAP kinase cascades are known in humans that lead to altered gene expression: ERK1/2, JNK, and p38 MAP kinase.

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**Table 1** Mitogen activated protein (MAP) kinases

<table>
<thead>
<tr>
<th>MAP kinase Isoform</th>
<th>Alternative name</th>
<th>Substrate</th>
<th>Phenotypes of MAP kinase knockout mice.</th>
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<tbody>
<tr>
<td>ERK 1</td>
<td>p44 MAPK</td>
<td>MAPKAP-K1, MNKs, MSKs, Elk1</td>
<td>Defective T cell development</td>
</tr>
<tr>
<td>ERK 2</td>
<td>p42 MAPK</td>
<td>MAPKAP-K1, MNKs, MSKs, Elk1</td>
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<tr>
<td>ERK 3α</td>
<td>p63 MAPK</td>
<td>MNKs, MSKs</td>
<td></td>
</tr>
<tr>
<td>ERK 3β</td>
<td>human ERK3</td>
<td>MNKs, MSKs</td>
<td></td>
</tr>
<tr>
<td>ERK 4</td>
<td>ERK1b</td>
<td>MNKs, MSKs</td>
<td></td>
</tr>
<tr>
<td>ERK 5</td>
<td></td>
<td>MNKs, MSKs</td>
<td></td>
</tr>
<tr>
<td>ERK 7</td>
<td></td>
<td>MNKs, MSKs</td>
<td></td>
</tr>
<tr>
<td>JNK 1</td>
<td>SAPKγ</td>
<td>c-Jun, JunD, ATF-2, Elk1</td>
<td>Defective T cell differentiation to Th2 cells</td>
</tr>
<tr>
<td>JNK 2</td>
<td>SAPKδ</td>
<td>c-Jun, JunD, ATF-2, Elk1</td>
<td>Defective T cell differentiation to Th1 cells</td>
</tr>
<tr>
<td>JNK 3</td>
<td>SAPKβ</td>
<td>c-Jun, JunD, ATF-2, Elk1</td>
<td>Resistance to excitotoxic neuronal cell death</td>
</tr>
<tr>
<td>p38α</td>
<td>CSBP, SAPK2 MPK2, RK, Mox2</td>
<td>MAPKAP/K2/3, MSKs, ATF-2, Elk1, MEF2c</td>
<td>Placental defect, insufficient production of erythropoietin</td>
</tr>
<tr>
<td>p38β</td>
<td>p38–2, p38β</td>
<td>MAPKAP/K2/3, MSKs, ATF-2</td>
<td></td>
</tr>
<tr>
<td>p38γ</td>
<td>ERK6, SAPK3</td>
<td>ATF2</td>
<td></td>
</tr>
<tr>
<td>p38δ</td>
<td>SAPK4</td>
<td>ATF2</td>
<td></td>
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</table>

ATF-2, activating transcription factor 2; ERK, extracellular signal regulated kinase; JNK, c-Jun NH2 terminal kinase; MAP, mitogen activated protein; MAPK, MAP kinase; MAPKAP, MAP kinase activated protein kinase; MSK, myocyte enhance factor; SAPK, stress activated protein kinase; MNKs, MARK activating protein kinases; MEF, myocyte enhance factor; CSBP, cytokine suppressive anti-inflammatory binding protein; RK, reactivating kinase.
The in vivo relevance of this phosphorylation is not yet clear. c-Jun, c-Fos, and activating transcription factor 2 (ATF-2) but members of this family that are phosphorylated by ERK1/2 include activating protein 1 (AP-1) family of transcription factors. Membrane dynamics in vivo is poorly understood. Most often an important role in the regulation of cell proliferation and apoptosis. Gene knockout experiments have illustrated the importance of the ERK1/2 pathway. Disruption of one of the three Raf proteins known to activate ERK1/2 as well as other MAP kinases target not only transcription factors but also membrane proteins (that is, phospholipase A2) and cytoplasmic proteins (that is, downstream kinases). Results from gene knockout experiments have illustrated the importance of the ERK1/2 pathway. Disruption of one of the three Raf proteins known to activate ERK1/2 is invariably fatal in mice. Also, when MEK1 was genetically targeted, embryonic death was observed with signs of tissue necrosis. Precisely how ERK1/2 affects cellular physiology in vivo is poorly understood. Most often an important role is attributed to ERK1/2 dependent regulation of the activating protein 1 (AP-1) family of transcription factors. Members of this family that are phosphorylated by ERK1/2 include c-Jun, c-Fos, and activating transcription factor 2 (ATF-2) but the in vivo relevance of this phosphorylation is not yet clear. Elk-1, which activates c-Fos, is another transcription protein that is phosphorylated by ERK1/2.

“ERK1/2 as well as other MAP kinases target not only transcription factors but also membrane proteins”

Although the primary role of ERK1/2 mediated signalling has long been thought to be restricted to cell growth and proliferation, it has become clear that several inflammatory processes involve ERK1/2 activation. Erk-1 deficient mice were normal and fertile but showed defective thymocyte maturation and reduced expression of α and β chains of the T cell receptor. This indicates that ERK activation is crucial for T cell activation, and this was reported to be mediated by the AP-1 family of transcription factors.

The JNK signal transduction pathway

The JNK signalling pathway is a cell stress activated pathway that is involved in the regulation of cell proliferation and apoptosis. JNK protein kinases are encoded by the three genes JNK1, JNK-2, and JNK-3, which are alternatively spliced to form the JNK isoforms (table 1). In parallel with ERK1/2, JNK appears to be essential for AP-1 activation caused by stress and exposure to various cytokines. The two MAPKKK proteins that act as upstream JNK activators are MKK7, which is primarily activated by cytokines (TNF, IL-1), and MKK4, primarily activated by environmental stress (fig 3). MAPKKK activators of JNK are composed of a large group of more than 12 intracellular proteins, including those of the MEKK group (MEKK 1–4), although it is not clear which are relevant to specific physiological stimuli. Duration and amplitude of JNK activation represents the balance between external stimuli and intracellular inactivation mechanisms. Four negative JNK regulatory factors have now been identified: MAP kinase phosphatase MKP7, heat shock protein 72, Evi1 oncoprotein, and nitric oxide. The two primary AP-1 transcription components that are phosphorylated by JNK are c-Jun and ATF-2.

“The JNK signalling pathway is a cell stress activated pathway that is involved in the regulation of cell proliferation and apoptosis”

The three genes JNK1–3 have been disrupted in mice; this results in defects in immune responses and apoptosis. Isolated embryonic fibroblasts demonstrated defective AP-1 transcription activity, decreased proliferation, and resistance to stress induced apoptosis. Gene knockout studies targeting MKK7...
showed that TNF activates JNK through MKK7 whereas basal activity of MKK4 is required for full activation of JNK in response to TNF. JNK2 was shown to have a crucial role in Th cell differentiation and cytokine production. JNK2 activation through inflammatory cytokines released from Th1 cells produced markedly reduced amounts of IFN-γ, a key cytokine for Th1 cells. The JNK signalling pathway has been implicated in a large variety of pathological conditions, including cancer, stroke, ischaemic heart disease, and inflammatory disorders, and has therefore been appreciated as an attractive candidate for drug development.

The p38 MAP kinase signal transduction pathway

The p38 MAP kinase pathway shares many similarities with the other MAP kinase cascades being associated with inflammation, cell growth, cell differentiation, and cell death. Murine p38 was first identified in 1994 as a kinase activated in response to bacterial lipopolysaccharide (LPS). To date, four p38 MAP kinase isoforms have been identified sharing about 60% homology (table 1), and two isoforms (p38α, p38β) are ubiquitously expressed. p38γ is predominantly expressed in skeletal muscle whereas p38δ gene expression is found in the lungs, kidneys, testis, pancreas, and small intestine. In most inflammatory cells, p38α is the major isoform that is activated. Extracellular stimuli of the p38 MAP kinase pathway include a variety of cytokines (IL-1, IL-2, IL-7, IL-17, IL-18, TGF-β, and TNF-α) and a number of pathogens that activate p38 through the different Toll receptors, including LPS, staphylococcal peptidoglycan, staphylococcal enterotoxin B, echovirus 1, and herpes simplex virus 1. Moreover, several growth factors (that is, granulocyte macrophage-colony stimulating factor, colony stimulating factor 1, erythropoietin) are capable of inducing p38 as well as environmental factors such as heat shock, changes in osmolarity, ultraviolet, oxygen radicals, and hypoxic states.

"p38 MAP kinase probably plays a central role in the regulation of a wide range of immunological responses"
antigen induced IL-2 secretion. Recently, Merck reported that a resorcylic acid lactone, L783277, also isolated from microbial extracts, inhibits MEK effectively in vitro. In models of traumatic brain injury, MEK inhibitors were beneficial. In a rat model of global brain ischaemic tolerance, inhibition of ERK activation after preconditioning ischaemia by PD98059 significantly prevented the inhibitory effects of preconditioning ischaemia on ischaemic injury and reduced inflammatory responses to Helicobacter pylori LPS in rats. Thus it should be interesting to observe the effects of such inhibitors in human disease.

**Inhibition of JNK**

No specific JNK inhibitor has entered clinical evaluation. SP600125, developed by Celgene, is an inhibitor of JNK2 that does not interfere with the ERK or p38 MAP kinase pathway and reduces paw swelling in a rat model of inflammatory arthritis. CEP1347, a compound that inhibits members of the so-called mixed lineage kinases which are upstream activators of the JNK pathway, is a potent anti-inflammatory compound in experimental arthritis. Moreover, in acute experimental cerulein pancreatitis, treatment with CEP1347 resulted in significant amelioration and reduction of pancreatic edema. A membrane permeable peptide inhibitor of JNK (JNKi) has not been tested in vivo but inhibits AP-1 activation in alveolar macrophages. Thus pharmacological JNK inhibition has important anti-inflammatory consequences and emerges as a promising approach for combatting inflammatory disease in human pathology.

**Inhibition of p38 MAP kinase**

Signalling through p38 is required for synthesis of several proinflammatory cytokines, and several more or less selective p38 inhibitors have been developed (fig 4). Elucidation of the structural aspects of inhibitor/kinase interaction by x ray crystallography, mutagenesis, and mechanistic enzymology has improved the potency and selectivity of these compounds. The anti-inflammatory agent pyridinylimidazole and its analogues (SB (SmithKline Beecham) compounds) were shown to suppress proinflammatory cytokines through inhibition of p38α and p38β in several animal models of inflammation. In vitro studies as well as models of gene disruption demonstrated that SB203580, a widely used p38 inhibitor, can regulate gene transcription of IL-12 and IFN-γ and thus also the Th1 type immune responses. A murine model of endotoxin shock, SB203580 reduced mortality. Furthermore, SB203580 showed beneficial effects in collagen induced arthritis in mice. In TNBS induced colitis, SB203580 did not ameliorate inflammation but suppressed the proinflammatory cytokines IL-12 and IFN-γ.

A potential anti-inflammatory drug is CNI-1493, a synthetic guanlyhydrzone which inhibits the phosphorylation of both p38 MAP kinase and JNK. CNI-1493 can suppress macrophage activation and the production of several proinflammatory cytokines, including TNF-α, IL-1, IL-6, macrophage inflammatory protein 1α, and macrophage inflammatory protein 1β. In animal models of endotox shock, adult respiratory distress syndrome, pancreatitis, and rheumatoid arthritis CNI-1493 showed protective effects. In a pilot study in Crohn's disease patients, CNI-1493 administration resulted in a significant decrease in Crohn's disease activity index as well as mucosal healing. This study suggests that JNK is the more relevant target for CNI-1493 treatment as JNK phosphorylation was inhibited more potently than p38 in LPS stimulated peripheral blood mononuclear cells in vitro, and in mucosal inflammatory cells in vivo. This hypothesis was further supported by recent findings in TNBS induced colitis in mice which revealed that although the p38 MAPK inhibitor SB203580 effectively inhibited p38 MAPK enzymatic activity in these mice, no attenuation of disease progression was observed. A large controlled dose finding multicentre study with CNI-1493 is underway.

"In a pilot study in Crohn's disease patients, CNI-1493 administration resulted in a significant decrease in Crohn's disease activity index as well as mucosal healing."
In rheumatoid arthritis, all three MAP kinase pathways have been linked to processes relevant for oncogenesis. More specifically, ERK activation is considered essential for entry into the cell cycle and thus mitogenesis. Inhibition of ERK may therefore be useful in inhibiting tumour growth. Activation of the JNK pathway is associated in various ways with the apoptosis processes, and modulators of the JNK pathway may become useful for induction of cancer cell death or sensitising cancer cells to apoptosis on radiation therapy or chemotherapy. p38 MAP kinase, with its obvious role in inflammation, is often considered as a target with respect to leukaemia. Nevertheless, in vivo data as to the efficacy of such inhibitors in patients or even in animal models of oncogenic disease are still relatively sparse. No in vivo data, either in humans or in rodent models of oncogenic disease, have as yet been reported with respect to either the JNK or p38 MAP kinase pathway. An important study by Sebolt-Leopold et al described the discovery of an orally active MEK inhibitor with substantial in vivo bioactivity in mice with colon carcinomas of both mouse and human origin. Th merall MEK inhibitors are currently undergoing clinical trials but not much data have, as yet, entered the public domain. Various inhibitors of Raf, which act upstream of MEK, have also been shown to reduce tumour growth in xenograft models encompassing tumours of the colon, lung, and pancreas but human data are still not available. The clinical effects of farnesyl transferase inhibitors, which target different variants of the even more upstream Ras proteins, have until now been somewhat disappointing. Hence the actual usefulness of targeting MAP kinase pathways for combating human cancer remains unproven.

CONCLUSIONS
Increased understanding of signal transduction mechanisms and gene regulation involved in immune responses has created opportunities for the discovery of novel therapeutic compounds useful in treating inflammatory disorders. These new “design drugs” seem attractive because they are capable not only of reducing a spectrum of proinflammatory cytokines but may be small molecules that can be administered orally. Although MAP kinases are necessary for life, the reported clinical side effects of MAP kinase inhibitors have not precluded further clinical development. Moreover, MAP kinase inhibitors have been used in combination with other immunosuppressive drugs, including biological therapy. Finally, production of oral MAP kinase inhibitors will not be as costly as, for example, antibody based therapies.

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