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Review

MAPK signalling pathways as molecular targets for anti-inflammatory therapy—from molecular mechanisms to therapeutic benefits

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Abstract

Excessive inflammation is becoming accepted as a critical factor in many human diseases, including inflammatory and autoimmune disorders, neurodegenerative conditions, infection, cardiovascular diseases, and cancer. Cerebral ischemia and neurodegenerative diseases are accompanied by a marked inflammatory reaction that is initiated by expression of cytokines, adhesion molecules, and other inflammatory mediators, including prostanoids and nitric oxide. This review discusses recent advances regarding the detrimental effects of inflammation, the regulation of inflammatory signalling pathways in various diseases, and the potential molecular targets for anti-inflammatory therapy. Mitogen-activated protein kinases (MAPKs) are a family of serine/threonine protein kinases that mediate fundamental biological processes and cellular responses to external stress signals. Increased activity of MAPK, in particular p38 MAPK, and their involvement in the regulation of the synthesis of inflammation mediators at the level of transcription and translation, make them potential targets for anti-inflammatory therapeutics. Inhibitors targeting p38 MAPK and JNK pathways have been developed, and preclinical data suggest that they exhibit anti-inflammatory activity. This review discusses how these novel drugs modulate the activity of the p38 MAPK and JNK signalling cascades, and exhibit anti-inflammatory effects in preclinical disease models, primarily through the inhibition of the expression of inflammatory mediators. Use of MAPK inhibitors emerges as an attractive strategy because they are capable of reducing both the synthesis of pro-inflammatory cytokines and their signalling. Moreover, many of these drugs are small molecules that can be administered orally, and initial results of clinical trials have shown clinical benefits in patients with chronic inflammatory disease.

Keywords: Inflammatory disease; Neuroinflammation; Pro-inflammatory cytokine; MAP kinases; Transcription factor; Immunosuppressant; Inhibitor

1. Introduction

Inflammation, a key process in the host defence system, is highly regulated in order to restrict its action to the time and place where it is necessary. Loss of control can lead to a number of diseases, including rheumatoid arthritis, chronic inflammatory bowel diseases, neurodegenerative disorders, and septic shock syndrome [1,2]. Triggered by a variety of physical, chemical, or biological agents, inflammation is a cumulative result of genetic susceptibility factors and multiple responses, both paracrine and autocrine in nature. Although the inflammatory responses are different in various diseases, they can be characterised by a common spectrum of genes and endogenous mediators involved, including growth factors, inflammatory cytokines such as interleukin 1 β (IL-1β), tumour necrosis factor (TNF)-α, interleukin-6 (IL-6), chemokines (Macrophage Inflammatory Factor—MIP-1α,β, IL-8), matrix metalloproteinases, and toxic molecules such as nitric oxide or free radicals [3,4].

Rheumatoid arthritis is a chronic and systemic disorder that is characterised by progressive destruction of articular cartilage and bone. The aetiology of rheumatoid arthritis has still not been elucidated but it is thought to be triggered by a combination of genetic susceptibility and exposure to environ-

Abbreviations: ARE, AU-rich element; ASK, Apoptosis Signal regulating Kinase; ATF-2, Activating Transcription Factor 2; CRE, Cyclic AMP Responsive Element; ERK, Extracellular signal regulated kinase; iNOS, inducible Nitric Oxide Synthase; JNK, c-Jun N-terminal Kinase; LPS, lipopolysaccharide; MEF-2C, Myocyte enhancer factor 2C; MAPKAP-K2/3, MAP kinase-activated protein kinase 2/3; MEK, MAP/ERK kinase; MKK, MAP kinase kinase; MLK, Mixed lineage kinase; NIK, NF-κB-inducing kinase; TAK1, Transforming growth factor-activated kinase 1; TNF, Tumor necrosis factor; TPL2, Tumor progression locus 2

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mental factors. TNF-α, IL-1β, -6, and -8 are significantly abundant in joint lesions of rheumatoid arthritis patients. These cytokines are mostly released from the macrophages that infiltrate joint lesions (for review, see [5,6]). Monoclonal antibodies against TNF-α or TNF-α receptor-Fc fusion protein suppress the symptoms and disease progress of rheumatoid arthritis [7–9]. Similarly, patients treated with the IL-1 receptor antagonist showed improvement in clinical studies [10].

Inflammatory bowel disease encompasses a number of chronic, relapsing inflammatory disorders involving the gastrointestinal tract. Ulcerative colitis and Crohn's disease are two entities of chronic inflammatory bowel diseases in which a dysregulated immune response triggered by products of the enteric bacterial flora, viral and, perhaps, dietary antigens, is one of the main pathogenic mechanisms [11]. TNF plays a central role in the initiation and amplification of the inflammatory reaction in Crohn's disease [12]. Monoclonal antibodies against TNF have proven clinically effective [13].

Tissue damage in acute and chronic neurodegenerative diseases is a result of a complex pathophysiological cascade which comprises a variety of distinct pathological events [14]. One of the common pathophysiological hallmarks of neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, HIV-associated dementia, brain trauma, and stroke, is microglial activation [15,16]. Resident non-neuronal brain cells respond rapidly to neuronal cell death and may have both deleterious and beneficial roles in neuronal damage. Microglial cells activated in vitro produce toxic reactive oxygen radicals and NO, substances that may directly damage neurons. Activated microglia release neurotoxic and pro-inflammatory cytokines such as FasL, TNF-α, IL-1, IL-6, INF-γ, and numerous chemokines [17–20]. Cytokines produced by microglia may further activate astrocytes that in turn become a source of neurotoxic cytokines. Growing evidence indicates that the inhibition of secretion or activity of IL-1β and TNF-α with neutralising antibodies or soluble cytokine receptors leads to a decrease in neuronal damage [21,22]. Knockout mice deficient in neuronal nitric oxide synthase [23], or IL-1β converting enzyme—ICE [21] are less vulnerable to toxic insult. The role of TNF-α in brain ischemia is controversial and probably depends on experimental conditions [24]. TNF-α is one of the mediators dramatically increased after brain injury that leads to the activation, proliferation, and hypertrophy of phagocytic cells and gliosis. Its inhibition by pharmacological agents, neutralising antibodies or soluble receptors has protective effects. In contrast, reports from in vitro studies and knock-out mice suggest rather beneficial effects of TNF-α (for a review see [22]).

Astrocytes, the major glial cell type in the brain, are important contributors to inflammatory immune responses within the brain. Astrocyte hypertrophy and proliferation (called reactive gliosis) is a widespread response to damage of neurons. Astrocytes produce several neurotrophic substances that regulate viability of neurons after ischemia, but they are also a source of pro-inflammatory (IL-1, IL-6) and cytotoxic cytokines (FasL, TNF-α, TGF-β). Activated astrocytes also produce toxic molecules such as reactive oxygen species and NO (for a review, see [25]).

2. MAPK involvement in regulation of crucial inflammation mediators

2.1. Activation of p38 MAPK signal transduction pathway during inflammation

In response to inflammatory stimuli that activate macrophages, intracellular signalling pathways are activated that carry the signal needed to activate the production of inflammatory mediators. Primary inflammatory stimuli (microbial products) and cytokines such as IL-1 β and TNF α, act through the Toll receptors, IL-1 receptor (TIR) family or the TNF receptor family, respectively. Activation of receptors triggers major intracellular signalling pathways: mitogen-activated protein kinase (MAPK) pathways [26–29], and the pathway leading to activation of the transcription factor nuclear factor kappa B (NF κB) [26,30]. TNF-α is a potent activator of NF-κB, which in turn is a potent inducer of TNF-α. This positive feedback is key to chronic inflammatory conditions such as rheumatoid arthritis and inflammatory bowel disease. Lipopolysaccharide (LPS), a component of bacterial wall and commonly used inducer of the monocyte/macrophage cell lineage, acting via Toll-like receptor 4 (TLR4), also stimulates mitogen-activated protein (MAP) kinase cascades and the pathway leading to activation of NF-κB.

Three major groups of distinctly regulated MAP kinase cascades are known in humans that lead to altered gene expression: ERK1/2, JNK, and p38 MAP kinase. ERK are activated by MAP kinase kinase (MKK) and MKK2, JNK by MKK4 and MKK7, and p38 MAP kinase by MKK3, MKK4, and MKK6 [31,32] (Fig. 1). Upon activation of the MAP kinases, transcription factors present in the cytoplasm or nucleus are phosphorylated and activated, leading to expression of target genes resulting in a biological response. It has been demonstrated that MAP kinases have overlapping substrate specificities and phosphorylation of regulatory sites is shared among multiple protein kinases. The multiple interactions between the different MAP kinase cascades serve to integrate the responses and activate separate sets of genes [28,31].

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 [28]. To date, four p38 MAP kinase isoforms have been identified sharing about 60% homology. Two isoforms (p38α, and p38β) are ubiquitously expressed, p38γ is predominantly expressed in skeletal muscle, whereas p38δ gene expression is found in the lung, kidney, testis, pancreas, and small intestine. p38 MAPK is activated by dual phosphorylation on Thr180 and Tyr182 by upstream MAPK kinases: MAP2K6 or MAP2K3 (MKK3/6), which are activated by upstream MAPKKKs, and stimulated by a variety of stimuli [31,32]. A MAPKK-independent mechanism of p38 activation involves TAB1 (transforming growth factor-β-activated protein kinase 1 (TAK1)-binding protein 1).

Extracellular stimuli of the p38 MAP kinase pathway include a variety of cytokines (IL-1α, IL-2, IL-7, IL-17, IL-