Pharmacological Potential of p38 MAPK Inhibitors

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Abstract A key component of the intracellular signaling pathways involved in cellular response to environmental stress and inflammatory cytokines is the p38 family of mitogen-activated protein kinases (MAPKs). Of the four isoforms of the p38 family of MAPKs identified thus far, p38α is the most characterized enzyme. Since the discovery of p38α MAPK as a target of a series of compounds that inhibited the production of inflammatory cytokines, an intense effort has been applied to further identify, develop, and refine highly potent and selective inhibitors of this enzyme. In addition, availability of p38α MAPK inhibitors has allowed the investigators to dissect this signaling pathway and to examine its role in various pathologies. A large body of biochemical as well as genetic evidence indicates a critical role of p38α MAPK in both the production of inflammatory cytokines such as interleukin (IL)-1 and tumor necrosis factor (TNF) and subsequent signaling initiated in response to these cytokines. This suggests that inhibition of p38α MAPK pathway will have utility in pathological settings where tissue inflammation and pro-inflammatory cytokines have been implicated. Indeed, several p38α MAPK inhibitors have been shown to be efficacious in preclinical animal models of a variety of diseases, including rheumatoid arthritis, pulmonary diseases, neuronal protection, and cancer. In the past few years, several groups have advanced inhibitors into early clinical studies for rheumatoid arthritis, but none thus far has reached the critical phase III efficacy stage. In this chapter, we re-
view the p38 MAPK pathway and pharmacological potential of p38α MAPK inhibitors in various pathologies with particular emphasis on inflammatory diseases.

**Keywords**  
p38 MAPK · Inhibitors · Inflammation · Interleukin 1 · Tumor necrosis factor · Cytokines · Rheumatoid arthritis · Respiratory · Neuronal

### 1 Introduction

The ability of living cells to respond to the multitude of signals emanating from its environment rests with a variety of signaling pathways inside the cell. The components involved and their assembly in a pathway are dependent upon the type, duration, and magnitude of the signal and ensure the appropriate integrating and processing of the signal resulting in a stimulus-specific response. One of the major intracellular signaling pathways is the mitogen-activated protein kinase (MAPK) pathway. A central component of this pathway is the MAPKs. The MAPK signaling cascade consists of three protein kinases (Pearson et al. 2001), MAPK and two upstream components, MAPK kinase (MAPKKK or MKK) and MAPKK kinase (MAPKKK) (Fig. 1). Three MAPK pathways have so far been described in mammalian cells. The first to be discovered was the extracellular signal-related kinases, ERK1 and ERK2. Subsequently, c-jun amino terminal kinase (JNK) and p38 MAPK

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**Fig. 1** p38 MAPK pathways with activators and substrates