Mitogen-activated protein kinases: A new therapeutic target in cardiac pathology

Táňa Ravingerová, Miroslav Barančík and Monika Strnisková
Institute for Heart Research, Slovak Academy of Sciences, Bratislava, Slovak Republic

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Abstract

Eukaryotic cells respond to different external stimuli by activation of mechanisms of cell signaling. One of the major systems participating in the transduction of signal from the cell membrane to nuclear and other intracellular targets is the highly conserved mitogen-activated protein kinase (MAPK) superfamily. The members of MAPK family are involved in the regulation of a large variety of cellular processes such as cell growth, differentiation, development, cell cycle, death and survival. Several MAPK subfamilies, each with apparently unique signaling pathway, have been identified in the mammalian myocardium. These cascades differ in their upstream activation sequence and in downstream substrate specificity. Each pathway follows the same conserved three-kinase module consisting of MAPK, MAPK kinase (MAPKK, MKK or MEK), and MAPK kinase kinase (MAPKKK, MEKK). The major groups of MAPKs found in cardiac tissue include the extracellular signal-regulated kinases (ERKs), the stress-activated/c-Jun NH2-terminal kinases (SAPK/JNKs), p38-MAPK, and ERK5/big MAPK 1 (BMK1). The ERKs are strongly activated by mitogenic and growth factors and by physical stress, whereas SAPK/JNKs and p38-MAPK can be activated by various cell stresses, such as hyperosmotic shock, metabolic stress or protein synthesis inhibitors, UV radiation, heat shock, cytokines, and ischemia. Activation of MAPKs family plays a key role in the pathogenesis of various processes in the heart, e.g. myocardial hypertrophy and its transition to heart failure, in ischemic and reperfusion injury, as well in the cardioprotection conferred by ischemia- or pharmacologically-induced preconditioning. The following approaches are currently utilized to elucidate the role of MAPKs in the myocardium: (i) studies of the effects of myocardial processes on the activity of these kinases; (ii) pharmacological modulations of MAPKs activity and evaluation of their impact on the (patho)physiological processes in the heart; (iii) gene targeting or expression of constitutively active and dominant-negative forms of enzymes (adenovirus-mediated gene transfer).

This review is focused on the regulatory role of MAPKs in the myocardium, with particular regard to their involvement in pathophysiological processes, such as myocardial hypertrophy and heart failure, ischemia/reperfusion injury, as well as in the mechanisms of cardioprotection. In addition, it summarizes current information on pharmacological modulations of MAPKs activity and their impact on the cardiac response to pathophysiological processes. (Mol Cell Biochem 247: 127–138, 2003)

Key words: mitogen-activated protein kinases, myocardium, hypertrophy, ischemia, preconditioning, cardioprotection

Introduction

The cardiomyocyte is a terminally differentiated cell that responds to numerous external stimuli by adaptive growth (hypertrophy) in the absence of cell division [1]. One of the characteristic features of this physiological response is an increased expression of proto-oncogenes c-fos and c-jun induced by low levels of stress [1]. Extracellular stimuli, such as growth factors, cytokines, physical and/or chemical stress, initiate signal transduction from the plasma membrane mediated by sequential phosphorylation and activation of specific components of MAPK cascades. The expression of MAPKs and their activity has been demonstrated in the heart cells of all animal species studied [2–7]. Since cardiac myo-
cytes cannot respond to mitogenic stimuli with cell division, these kinase systems gained a different function and are involved mainly in the mechanisms of response to stress and cell survival and death (apoptosis). Regulation of gene expression in response to extracellular stimuli belongs to one of the most explored roles of MAPKs in the mammalian myocardium.

The three major MAPKs cascades identified in the myocardium are the ERKs and two stress-activated MAPKs subfamilies – SAPK/JNK and p38 MAPKs (Fig. 1). These kinases are encoded by different genes and differ in the amino acid activation motif. Each cascade consists of the same three-kinase module [8]. Activation of upstream located MAPK kinase kinase (MEKK) is followed by phosphorylation of MAPK kinase (MKK or MEK) on serine/threonine residues. Activation of the MAPK by MKK requires phosphorylation of threonine and tyrosine residues [9]. The MAPKs themselves are proline-directed serine/threonine kinases, phosphorylating serine and threonine residues [9, 10].

Differences in upstream activation mechanisms and substrates specificity do not exclude parallel activation of different MAPK cascades and their crosstalk at various levels (upstream of the cascades, within the cascades, within the substrates). This is particularly important for the transcriptional regulation in the heart, since MAPKs phosphorylate and increase transactivating/DNA-binding activity of several transcription factors in a cooperative way [11–14].

MAPK family and its regulatory role in the myocardium

**Extracellular signal-regulated (protein) kinases (ERKs)**

This cascade is the most well studied. The activation of the ERKs subfamily occurs in response to mitogenic and growth factors acting through receptor protein tyrosine kinases or G protein-coupled receptors [9, 15]. Recently, an activation of ERK1/2 and translocation to the nucleus has been demonstrated in isolated rat heart in response to a physical stretch induced by an increase in intraventricular pressure [16]. In isolated rat cardiomyocytes, activation of ERK pathway was shown to be initiated by enhanced calcium entry into the cells through L-type Ca\(^{2+}\) channels, and signaling mechanisms involved phosphorylation of proline-rich tyrosine kinase 2 (Pyk2) and epidermal growth factor receptor (EGFR) [17]. An immediate upstream regulator of the ERKs is MEK 1/2. Activation of MEK involves the small G-protein (Ras), the 74 kD protein Ser/Thr kinase, the Raf-1 kinase and some kinases, which might belong to the protein kinase C family [18–20]. Mechanism of MEK activation involves phosphorylation on two Ser residues within MEK subdomains VII and VIII. Activated MEKs demonstrate a high degree of specificity for the native form of their downstream substrates, the ERK 1 and ERK 2. The phosphorylation motif of ERKs is Thr-Glu-Tyr [21].

![Fig. 1. A schematic diagram of the three major mitogen-activated protein kinase (MAPK) signaling pathways. Main members of MAPK family (p38-MAPK, SAPK/JNK and ERK1/2) and upstream activators of each cascade (MEK and MEKK) are indicated in bold-faced type. Abbreviations: PAK – p21-activated kinase; DLK – dual leucine zipper-bearing kinase; MLK3 – mixed-lineage kinase 3. See text for other abbreviations and explanation.](image-url)