Mitogen-activated protein kinase (MAPK) in cardiac tissues

Carine Page and Anton F. Doubell

Department of Internal Medicine, Faculty of Medicine, University of Stellenbosch, Tygerberg 7505, South Africa

Abstract

Mitogen-activated protein kinase (MAPK) has recently emerged as a prominent role player in intracellular signalling in the ventricular myocyte with attention being focussed on its possible role in the development of ventricular hypertrophy. It is becoming clear that MAPK is also active in other cells of cardiac origin such as cardiac fibroblasts and possible functions of this signalling pathway in the heart have yet to be explored. In this report the mammalian MAPK pathway is briefly outlined, before reviewing current knowledge of the MAPK pathway in cardiac tissue (ventricular myocytes, vascular smooth muscle cells and cardiac fibroblasts). New data is also presented on the presence and activity of MAPK in two additional cardiac cell types namely atrial myocytes and vascular endothelial cells from the coronary microcirculation. (Mol Cell Biochem 157: 49-57, 1996)

Key words: MAP kinase, cardiac, atrial, endothelial

Introduction

Several recent reports have focussed attention on the presence of mitogen-activated protein kinase (MAPK) in ventricular myocytes and have investigated the role of this signalling pathway in the development of hypertrophy [1-5]. Very little has been reported regarding the presence of MAPK in other cardiac cell types [6-10] or the role of this kinase cascade in the heart in processes other than hypertrophy. In non-cardiac tissue a wealth of information has been accumulated about mammalian MAPK [11-14] and even greater detail is being added by studying this signalling pathway in lower eukaryotes such as yeasts [15, 16].

In this paper we will briefly outline the mammalian MAPK pathway with reference to knowledge obtained in lower eukaryotes where necessary, before reviewing current knowledge of the MAPK pathway in cardiac tissue (ventricular myocytes, vascular smooth muscle cells and cardiac fibroblasts) and presenting new data on MAPK activity in atrial myocytes and vascular endothelial cells from the coronary microcirculation.

The basic MAPK pathway

MAPKs are important intermediates relaying signals originating from many types of cell surface receptors to intracellular targets. The final common pathway activated by these signals involves a protein kinase cascade comprising of MAPK kinase kinase (also referred to as MEKK, i.e. MAPK/ERK kinase kinase), MAPK kinase (also referred to as MEK, i.e. MAPK/ERK kinase) and MAPK (Fig. 1). A number of MAPKKKs have been identified including Raf-1 [17], MEKK [18] and Mos [19]. In mammalian cells only the extracellular signal-regulated kinase (ERK) isoforms of MAPKs have been studied in detail. MAPK requires dual phosphorylation on a tyrosine and a threonine residue [12]) to be activated. The hallmark sequence of the MAPK family is a T-x-Y motif [12], where T represents threonine, Y represents tyrosine and x varies depending on the member of the MAPK family. In the case of ERK1 and ERK2 x represents glutamic acid (E). MAPK in turn phosphorylates target proteins on proline directed serine/threonine residues. Known targets of this kinase (Fig. 2) include cell surface proteins such as the epidermal growth factor receptor (EGF-R) and cytoplasmic phospholipase A2 (cPLA2) [20], kinases upstream of MAPK such as MAPKKK (c-Raf) and MAPKK (presumably regulating the pathway via feedback activation/inhibition) and other kinases downstream of MAPK such as MAPKAP kinase-2 and S6 kinase (p90rSk) as well as nuclear transcription factors such as c-Myc, c-Jun, NF-IL6, P62CTF/Elk-1 and ATF-2. Two other targets of note are the cytoskeletal proteins (microtubule associated proteins such as Tau) and myelin basic protein (MBP) used as substrate for in vitro MAPK
Fig. 1. Basic components of the classical MAPK pathway. Binding of various agonists, such as PDGF, to their cell surface receptors can activate the MAPK cascade. The basic components of the cascade depicted here include Ras, MAPKKK (c-Raf or MEKK), MAPKK (MEK) and MAPK (ERK1 and ERK2). The hallmark of MAPK is its dual phosphorylation on a tyrosine (Y) and a threonine (T) residue for activation, the consensus sequence for phosphorylation being \( ...T-x-Y... \). In the case of ERK1 and ERK2 \( x \) represents glutamic acid (E). MAPK, mitogen-activated protein kinase; MEK, MAPK/ERK kinase; ERK, extracellular signal-regulated kinase.

Fig. 2. Signal transduction through the MAPK pathway following activation of different receptor families. Ligand binding to a receptor tyrosine kinase (RTK) such as the epidermal growth factor receptor (EGF-R) activates the MAPK cascade. The initiating event is the activation of Ras via two intermediary proteins Grb2 and mSOS leading to localized activation of c-Raf to the cell membrane and activation of c-Raf. Raf then functions as a MAPKKK leading to activation of the rest of the kinase cascade as depicted in Fig. 1. Ligand binding to a seven transmembrane spanning receptor (STMR) (coupled to a heterotrimeric G-protein) such as acetylcholine binding to the \( M_3 \) muscarinic acetylcholine receptor can also activate the MAPK cascade, possibly also via Ras activation or through activation of MEKK. The activated MAPK will then modulate various target proteins (the list of substrates shown is not complete) carrying the necessary motif \( ...S/T-E... \) resulting in proline-directed serine or threonine phosphorylation. EGF-R, epidermal growth factor receptor; cPLA2, cytoplasmic phospholipase A2; MAPKAP-K2, MAPK activating protein kinase-2; TCF, ternary complex factor; MBP, myelin basic protein.

Parallel kinase cascades of the MAPK family

In the yeast *Saccharomyces cerevisiae* three signalling pathways employing MAPK homologs have been identified regulating three distinct functions namely the pheromone mating response, cell-wall synthesis and sensing hyperosmotic environments, with FUS3/KSS1, MPK1 and HOG1 being the MAPK homologues for the three pathways respectively. The striking feature of these pathways in the yeast is that they regulate these functions independently of one another i.e. elimination of a specific kinase in one pathway does not affect the other two pathways [15]. This pathway specificity is probably maintained by the target specificity of the various kinases as well as macromolecular complex formation by