Progress in Biophysics and Molecular Biology 98 (2008) 238–250

Contents lists available at ScienceDirect

Progress in Biophysics and Molecular Biology

journal homepage: www.elsevier.com/locate/pbiomolbio

Review

Regulation of cardiac excitation and contraction by p21 activated kinase-1

Yunbo Ke [a], Ming Lei [b], R. John Solaro [a,*]

[a] The Department of Physiology and Biophysics and Center for Cardiovascular Research, University of Illinois at Chicago, College of Medicine, Room 202, COMRB, 835 South Wolcott Avenue, Chicago, IL 60612, USA
[b] Division of Cardiovascular and Endocrine Science, School of Clinical and Laboratory Sciences, University of Manchester, Room 310, Core Technology Facility, 46 Grafton Street, Manchester, UK

ARTICLE INFO

Article history:
Available online 24 January 2009

Keywords:
Protein phosphatase 2A
L-type Ca^{2+}-channel
Sarcomeric protein phosphorylation
Ryanodine receptor

ABSTRACT

Cardiac excitation and contraction are regulated by a variety of signaling molecules. Central to the regulatory scheme are protein kinases and phosphatases that carry out reversible phosphorylation of different effectors. The process of β-adrenergic stimulation mediated by cAMP dependent protein kinase (PKA) forms a well-known pathway considered as the most significant control mechanism in excitation and contraction as well as many other regulatory mechanisms in cardiac function. However, although dephosphorylation pathways are critical to these regulatory processes, signaling to phosphatases is relatively poorly understood. Emerging evidence indicates that regulation of phosphatases, which dampen the effect of β-adrenergic stimulation, is also important. We review here functional studies of p21 activated kinase-1 (Pak1) and its potential role as an upstream signal for protein phosphatase PP2A in the heart. Pak1 is a serine/threonine protein kinase directly activated by the small GTPases Cdc42 and Rac1. Pak1 is highly expressed in different regions of the heart and modulates the activities of ion channels, sarcomeric proteins, and other phosphoproteins through up-regulation of PP2A activity. Coordination of Pak1 and PP2A activities is not only potentially involved in regulation of normal cardiac function, but is likely to be important in patho-physiological conditions.

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Abbreviations: AC, denylate cyclase; Ad, adenovirus; BK channel, Ca^{2+}-activated K^+ currents; B(PR55), PP2A regulatory subunits; B′(PR61), PP2A regulatory subunits; B″(PR72/130), PP2A regulatory subunits; B‴(PR93/110), PP2A regulatory subunits; cAMP, cyclic AMP; Cla4, a *Saccharomyces cerevisiae* Cdc42p-activated kinase; cTnI, cardiac troponin I, the inhibitory element of troponin complex; Cav1.2, a L-type Ca channel; CICR, Ca^{2+} induced Ca^{2+} release; CREB, cAMP-responsive binding protein, a transcription factor; DHPR, dihydropyridin receptor, L-type Ca channel; DI, dimerization domain of Pak1; F-actin, filamentous actin, polymerized actin; FKBP12.6, a FK binding protein, accessory protein of ryanodine receptors; GPCR, G protein coupled receptor; GEF, G protein exchange factor; Gi, the inhibitory large G protein; Gs, the stimulatory large G protein; GST, glutathione *S*-transferase; HERG, the human either-a-go-go-related gene or gene product, a potassium channel; Ik(ach), acetylcholine-gated potassium current; Ik(ado), adenosine (ado) induced muscarinic potassium current; I(ks), slow delayed rectifier potassium current; ISO, isoproterenol; KCNQ1-KCNE1, an I(ks) channel; Kv11.1, (ERG1) K+ channels; LPA, lysophosphatidic acid; MAP kinase, mitogen activated protein kinase; $MLC_{20,}$ myosin regulatory light chain; MLCK, myosin light chain kinase; Mst1, mammalian Ste20-like kinase; MyBP-C, myosin binding protein C; NCX, sodium/calcium exchanger; NFκB, kappa immunoglobulin enhancer-binding protein, a transcription factor; Nie115, a cell line derived from neurolastoma; Pak, p21 activated kinase; PBD, p21 binding domain; PKA, cAMP dependent protein kinase; PLB, phospholamban; PP1, protein phosphatase 1; PP2A, protein phosphatase 2A; ROS, reactive oxygen species; RyR, ryanodine receptor; SA node, sino-atrial node; Serca2, a sarco/endoplasmic reticulum Ca^{2+}-ATPase isoform; SR, sarcoplasmic reticulum; ssTnI, slow skeletal troponin I; SV40, simian virus 40; 3T3, a cell line derived from mouse fibroblasts; Ste20, a yeast protein kinase homologue of Cla4; Tg, transgenic; TnC, Troponin C; VT, ventricular tachyarrhythmia.

* Correspondence to: R. John Solaro, Department of Physiology and Biophysics (M/C 901), The University of Illinois at Chicago, College of Medicine, 835 South Wolcott Avenue, Chicago, IL 60612, USA. Tel.: +1 312 996 7620; fax: +1 312 996 1414.
E-mail address: solarorj@uic.edu (R.J. Solaro).

0079-6107/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.pbiomolbio.2009.01.007

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1. Introduction

Studies in the heart first elucidated effects and key proteins in major signaling by adrenergic and cholinergic pathways. Transduction of these signals involves reversible phosphorylation of proteins controlling ion channels, exchangers and pumps, sarcomeric and cytoskeletal function, energy metabolism, and gene transcription and translation. Kinase cascades that phosphorylate these proteins are relatively well worked out compared to the phosphatases that dephosphorylate these proteins. Moreover, modulation of the activity of phosphatases in the integrative biology of control of cardiac dynamics remains poorly understood. There is some understanding of control of phosphatases such as calcineurin by Ca^{2+}/calmodulin and protein phosphatase 1 (PP1) by PKA and inhibitor 1, but there is little understanding of signaling to protein phosphatase 2A (PP2A), a major cardiac phosphatase. We review here emerging evidence indicating that p21 activated kinase-1 (Pak1), a serine/threonine protein kinase directly activated by Cdc42 and Rac1 is an important signaling molecule potentially involved in major cardiac processes regulating excitation and contraction in healthy and disordered hearts.

1.1. Discovery

Studies on the Rho family of small GTPases including RhoA, Cdc42 and Rac1, which have diverse functions in mammalian cells, such as modulation of ROS (reactive oxygen species) (Knaus et al., 1991; Mizuno et al., 1992), regulation of cell proliferation and differentiation, apoptosis, and cytoskeletal reorganization (Hall, 1992; Ridley, 1995) led to the identification of Pak1. Pak1 was discovered in rat brain as a major binding partner for Cdc42 and Rac1 by protein overlay assay. Both the kinase activity and autophosphorylation of Pak1 *in vitro* increase significantly upon binding to the small G proteins (Manser et al., 1994).

Pak1 is a member of a family of serine/threonine protein kinases exhibiting direct activation by Cdc42 and Rac1. Pak1, 2 and 3 belong to group I of the Paks and share substantial sequence homology with each other, especially in their catalytic domains (Jaffer and Chernoff, 2002) (Fig. 1). Actually, in early studies Paks had been isolated from rabbit reticulocyte with unusually low kinase activities. When treated with proteases, the kinase activities increased significantly (Tahara and Traugh, 1981). A **p**rotease **a**ctivated **k**inase (PakI) phosphorylates myosin regulatory light chain from smooth and skeletal muscle cells (Tuazon et al., 1982; Tuazon and Traugh, 1984). Unlike PKA and PKG, the Pak activities are independent of cyclic nucleotides (Tahara and Traugh, 1981). Molecular cloning of the protease activated kinases indicates that they are identical with the small G protein activated kinases (Jakobi et al., 1996).

Pak1 induces the same cytoskeletal changes as its upstream activators Cdc42 and Rac1, such as dissolution of stress fibers and focal adhesion complexes, formation of filapodia, lamellipodia and membrane ruffles in mammalian cells (Manser et al., 1997; Sells et al., 1997). This has led to speculation for a potential role of Pak1 in cardiac remodeling (Sussman et al., 2000).

1.2. Structure

Pak1 protein is divided into an N-terminal regulatory domain and a C-terminal catalytic domain, each is about the half of the enzyme in amino acid sequence (Fig. 1). Even though Pak1 has very low sequence similarity with PKA, the prototype of all the serine/threonine protein kinases, Pak1 and PKA still share substantially similar kinase motifs in their catalytic domains. As with many other serine/threonine protein kinases, such as Mek1, PKA and PKC, Pak1 contains an activation loop in its catalytic domain and an autophosphorylation site inside the loop (Lei et al., 2000; Manser et al., 1997). The N-terminal half of Pak1 contains a few regulatory sequences. The p21 binding domain (PBD) is upstream of and partially overlaps with a kinase inhibitory domain that imposes an inhibitory effect on the catalytic activity by stabilizing an autoinhibitory configuration of the kinase. Sequence upstream of the PBD is involved in Pak1 dimerization (DI). The boundary between DI and PBD is not clear (Jaffer and Chernoff, 2002; Lei et al., 2000) (Fig. 1).

There are five proline-rich motifs scattered over the N-terminal region of Pak1. Some of these proline-rich motifs are followed by

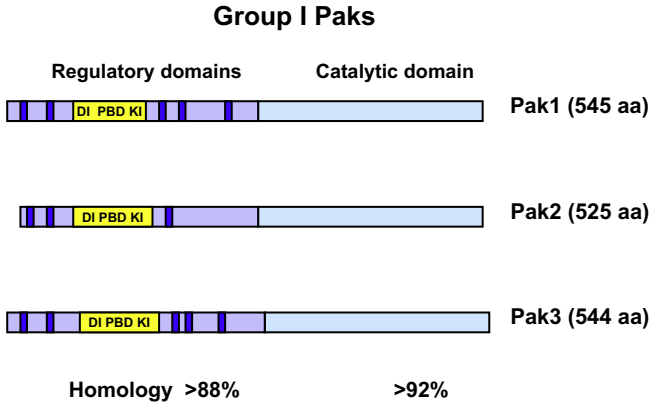

Fig. 1. The group I p21 activated kinases include Pak1 (α-Pak), Pak2 (γ-Pak) and Pak3 (β-Pak). DI—dimerization domain, PBD—p21 binding domain, KI—kinase inhibitory domain. ▮—proline-rich sequence, aa—amino acids. Both the regulatory and the catalytic domains of group I Paks are highly homologous to each other.

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