RHO GTPases activate PAKs

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references


Reactome database release: 72

This document contains 1 pathway and 15 reactions (see Table of Contents)
The PAKs (p21-activated kinases) are a family of serine/threonine kinases mainly implicated in cytoskeletal rearrangements. All PAKs share a conserved catalytic domain located at the carboxyl terminus and a highly conserved motif in the amino terminus known as p21-binding domain (PBD) or Cdc42/Rac interactive binding (CRIB) domain. There are six mammalian PAKs that can be divided into two classes: class I (or conventional) PAKs (PAK1-3) and class II PAKs (PAK4-6). Conventional PAKs are important regulators of cytoskeletal dynamics and cell motility and are additionally implicated in transcription through MAPK (mitogen-activated protein kinase) cascades, death and survival signaling and cell cycle progression (Chan and Manser 2012).

PAK1, PAK2 and PAK3 are direct effectors of RAC1 and CDC42 GTPases. RAC1 and CDC42 bind to the CRIB domain. This binding induces a conformational change that disrupts inactive PAK homodimers and relieves autoinhibition of the catalytic carboxyl terminal domain (Manser et al. 1994, Manser et al. 1995, Zhang et al. 1998, Lei et al. 2000, Parrini et al. 2002; reviewed by Daniels and Bokoch 1999, Szczepanowska 2009). Autophosphorylation of a conserved threonine residue in the catalytic domain of PAKs (T423 in PAK1, T402 in PAK2 and T436 in PAK3) is necessary for the kinase activity of PAK1, PAK2 and PAK3. Autophosphorylation of PAK1 serine residue S144, PAK2 serine residue S141, and PAK3 serine residue S154 disrupts association of PAKs with RAC1 or CDC42 and enhances kinase activity (Lei et al. 2000, Chong et al. 2001, Parrini et al. 2002, Jung and Traugh 2005, Wang et al. 2011). LIMK1 is one of the downstream targets of PAK1 and is activated through PAK1-mediated phosphorylation of the threonine residue T508 within its activation loop (Edwards et al. 1999). Further targets are the myosin regulatory light chain (MRLC), myosin light chain kinase (MLCK), filamin, cortactin, p41Arc (a subunit of the Arp2/3 complex), caldesmon, paxillin and RhoGDI, to mention a few (Szczepanowska 2009).

Class II PAKs also have a CRIB domain, but lack a defined autoinhibitory domain and proline-rich regions. They do not require GTPases for their kinase activity, but their interaction with RAC or CDC42 af-
fects their subcellular localization. Only conventional PAKs will be annotated here.

**Literature references**

Parrini, MC., Lei, M., Harrison, SC., Mayer, BJ. (2002). Pak1 kinase homodimers are autoinhibited in trans and dissociated upon activation by Cdc42 and Rac1. *Mol Cell*, 9, 73-83.


**Editions**

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RAC1 and CDC42 activate PAK1

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