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Gene Section
Mini Review

PAK2 (p21 protein (Cdc42/Rac)-activated kinase 2)

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Identity

Other names: PAK65; PAKgamma

HGNC (Hugo): PAK2

Location: 3q29

DNA/RNA

Description

Pak2 gene at 193763319 to 193859670 bp from pter contains 96352 bases and 34 exons. Pak2 gene at the alternative location starts at 196466728 and ends at 196559518 bp from pter. The PAK2 gene in this location contains 20 exons.

Protein

Description

Pak2 has an N-terminal regulatory domain and a C-terminal catalytic domain. In the regulatory domain, Pak2 have several conserved regions, including an autoinhibitory domain (AID), a p21-binding domain (PBD), dimerization domain, proline-rich regions, and an acidic region. The schematic structure of Pak2 is shown in figure above. The catalytic domain of Pak is a conserved bilobal structure in most of the protein kinases.

Expression

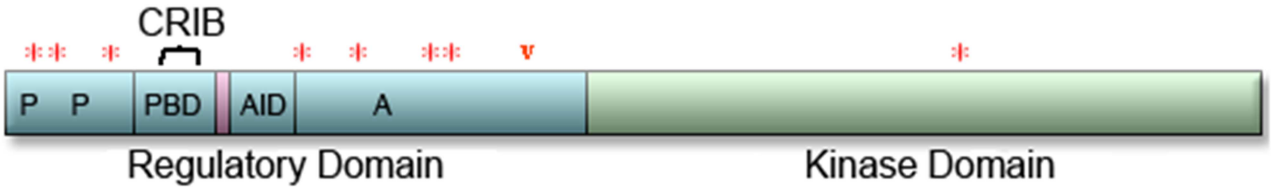
Pak2 is 58.8 kDa (524 residues) and expressed ubiquitously in mammalian cells.

Function

PAK activation is through disruption of autoinhibition, followed by autophosphorylation. In the inactive state, the AID interacts with the catalytic domain to inhibit its kinase activity. GTP-bound Cdc42 can disrupt autoinhibition, which, in turn, leads to autophosphorylation and activation of PAK. Pak2's basal autophosphorylation activity is observed and Pak2 is autophosphorylated at 5 sites, serines 19, 20, 55, 192 and 197. Additional three phosphorylation sites (serines 141 and 165 and threonine 402) are autophosphorylated in the presence of Cdc42(GTP) and ATP. Autophosphorylation of Thr402 in the activation loop is required for the kinase activity of Pak2.

Pak2 can be activated in response to a lot of stresses. Moderate stresses, like hyperosmolarity, ionizing radiation, DNA-damaging agents and serum-deprivation, induce Pak2 activation in cells and lead to cell cycle arrest at G2/M. Activated Pak2 inhibits translation by phosphorylation of various substrates. Pak2 has specific protein substrates, e.g. histone 4, myosin light chain (MLC), prolactin, c-Abl, eukaryote translation initiation factor 3 (eIF3), eIF4B, eIF4G, and Mnk1. Pak2 recognizes the consensus sequence (K/RRXS).

Pak2 is the only member of the PAK family that is directly activated by caspase 3. When Pak2 is cleaved and activated by caspase 3, Pak2 promotes the morphological and biochemical changes of apoptosis. The pro-apoptosis protease, caspase 3 cleaves Pak2 after Asp 212, and thus produces a p27 fragment containing primarily the regulatory domain, and a p34 fragment containing a small piece of the regulatory domain and the entire catalytic domain. Autophosphorylation results in a constitutively active p34 kinase domain.



The Linear schematic of Pak2. Functional domains, including proline rich regions (P), acidic region (A), p21-binding domain (PBD), Cdc42 and Rac interaction and binding sequence (CRIB) and autoinhibitory domain (AID) are designated. Autophosphorylation sites (*) and caspase 3 cleavage site (v) are marked. The regulatory domain is blue; the protein kinase domain is green; the overlapping region between PBD and AID is pink.

The nuclear import signal (245-251) is required for nuclear localization. Disruption of the region (197-246), containing nuclear export signal results in the nuclear localization of the Pak2 p34 fragment.

Homology

Pak1, Pak2 and Pak3 are highly homologous. The primary sequence of human Pak2 is 72 % identical to Pak1 and 71 % identical to Pak3.

Mutations

Note

None is reported.

Implicated in

Tumors

Prognosis

Huang (2004) showed Pak2 is a negative regulator of Myc and suggested Pak2 may be the product of a tumor suppressor gene. Coniglio (2008) reported Pak2 mediates tumor invasion in breast carcinoma cells. Inhibition of RhoA in Pak2-depleted cells decreases MLC phosphorylation and restores cell invasion. Also, the NF2 tumor suppressor Merlin is a substrate of Pak2. Wilkes (2009) showed that Erbin regulates the function of Merlin through Pak2 binding to Merlin.

Immunodeficiency

Note

Human immunodeficiency virus type 1 HIV-1.

Prognosis

Human immunodeficiency virus type 1 Nef associates with a active Pak2 independently of binding to Nck or PIX. Nef recruits the GEF Vav1 to plasma membrane to associate with Pak2.

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