Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section

Mini Review

PAK1 (p21/Cdc42/Rac1-activated kinase 1 (STE20 homolog, yeast))

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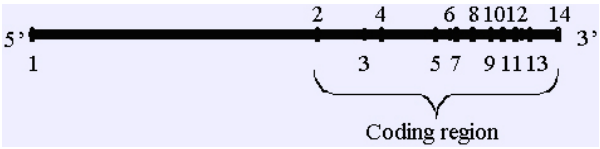
Identity

Hugo: PAK1
Other names: Alpha-PAK; MGC130000; MGC130001; P65-PAK; PAK-1; PAKalpha
Location: 11q13.5
Local order: centromere - MYO7A - GDPD4 - LOC387791 - PAK1 - DFFZp434E1119 - FLJ38894 - AQP11.
Note: PAK1 encodes a serine/threonine specific protein kinase that is a member of the PAK branch of the STE20 family. PAK1 plays a role in cell survival, polarity, and motility, and may have oncogenic function when overexpressed.

DNA/RNA



The alignment of PAK1 mRNA to its genomic sequence.

Description

The PAK1 gene contains 14 exons. The sizes of the exons 1-14 are 189, 100, 129, 147, 37, 119, 174, 63, 48, 112, 117, 99, 196, 137, and 86 bps. Exon 2 contains the translation initation ATG, and a few additional codons. Exon 13 contains the stop codon. Other features of the PAK1 gene, such as promoters or enhancer elements, have not been described.

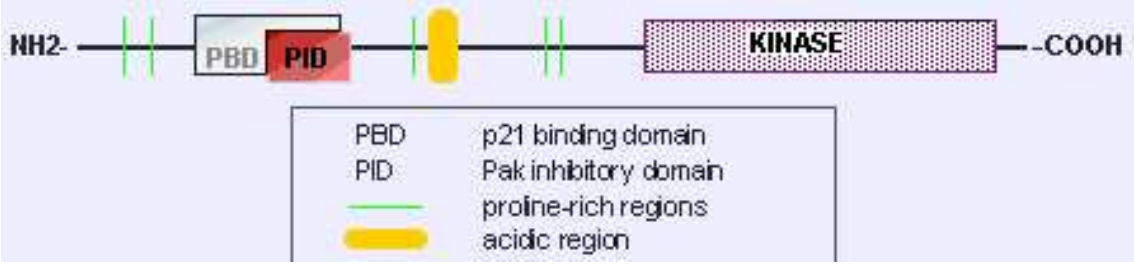
Transcription

PAK1 expression is particularly high in the brain. Other tissues which have reasonably high levels of PAK1 expression include spleen and skeletal muscle. The mRNA size is 1945 bps.

Protein

Description

PAK1 is a highly conserved serine/threonine protein kinase of 545 amino acids and is a member of the PAK group of the STE20 family of serine/threonine protein kinases. Pak1 is active in a monomeric form; the non-active form is an autoinhibited homodimer. Pak1 contains a regulatory N-terminal regulatory domain and non-classical SH3-binding site for the PIX family of proteins (PXP). Pak1 binds to activated forms of the GTPases Cdc42 and Rac. Pak1 homodimerizes through a motif adjacent to the p21-binding domain, and is autoinhibited.



Upon binding to Cdc42 or Rac, Pak1 is activated and autophosphorylates. Pak1 has dozens of substrates, activating cytoskeletal and transcription pathways that enhance cell motility, proliferation, and survival.

Expression

PAK1 is highly expressed in epithelium of tongue and larynx and in thyroid gland, expression also found in central nervous system (brain).

Localisation

Under basal conditions, Pak1 localizes to the cytosol. Upon growth factor stimulation, Pak1 is recruited to the plasma membrane as well as the nucleus.

Function

Cell survival and proliferation

Homology

Similar to STE20 in budding yeast and PAK1 in fission yeast. Human PAK1 complements both these yeast genes.

Mutations

Note: No mutations in the PAK1 gene have been reported.

Implicated in

Cancers

Disease

There is emerging evidence that the Pak family may play a key role in several human malignancies, including breast, ovarian, head and neck, colon, thyroid, and renal cancer. In human breast cancer, the expression level of Pak1 correlates with the tumor grade, with higher expression in less differentiated ductal carcinomas of the breast (grade III tumors) than in grade II and grade I tumors.
Pak1 overexpression is also associated with tamoxifen resistance in breast cancer. In human tumors, Pak1 is not itself activated by mutation: rather, Pak1 is overexpressed by unknown mechanisms. Pak1 may also play a role in transformation by Kaposi's sarcoma-associated herpes virus, which induces Kaposi's sarcoma and primary effusion lymphomas.

Prognosis

Recently, it has been shown that the level of phosphorylated (activated) Pak1 Level in the cytoplasm correlates with shorter survival time in patients with glioblastoma. As noted above, Pak1 expression may also correlate with tamoxifen resistance in breast cancer.

References

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