

Gene Section

Review

CRK (v-crk sarcoma virus CT10 oncogene homolog (avian))

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Published in Atlas Database: March 2012

Online updated version : <http://AtlasGeneticsOncology.org/Genes/CRKID40149ch17p13.html>

DOI: 10.4267/2042/47483

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Identity

Other names: CRKII, p40

HGNC (Hugo): CRK

Location: 17p13.3

Note

CT10 regulator of kinase.

DNA/RNA

Note

Crk belongs to an adaptor family of protein mostly composed of SH2 (src homology 2) and SH3 domains.

Description

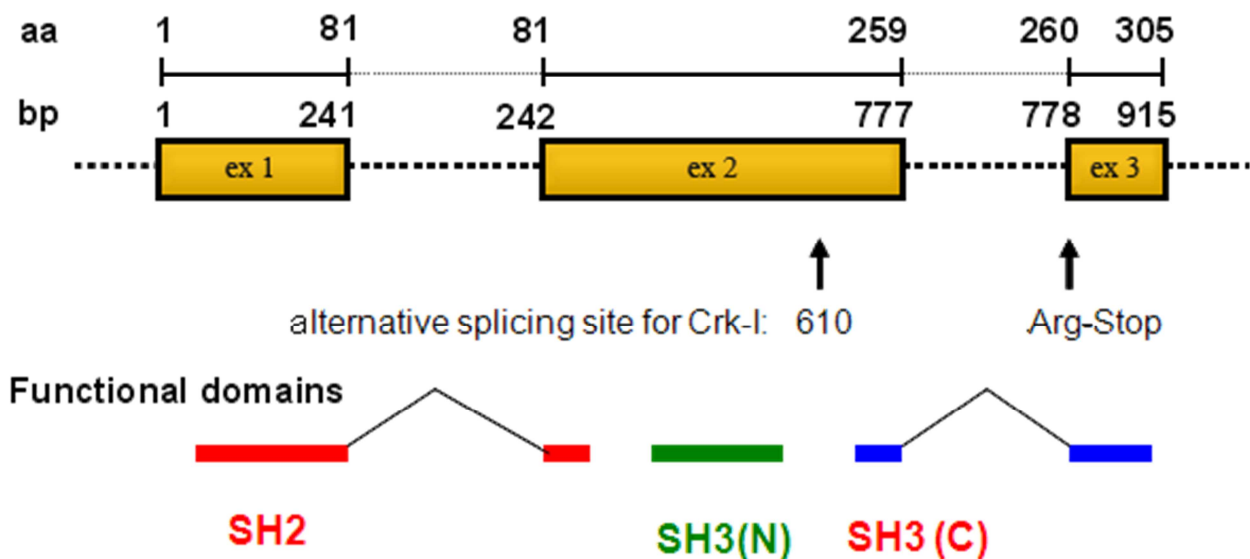
The human genomic DNA sequence contains 3 exons.

Transcription

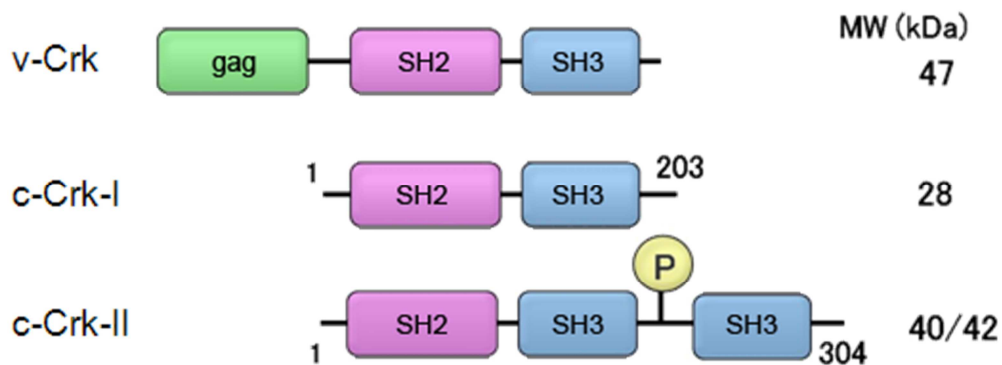
The length of open reading frame of transcript is 912 mer and translated to a 304 residues protein referred as c-Crk-II. By alternative splicing, 610-778 were deleted and truncated protein encoding 203 amino acids protein as c-Crk-I was generated. Recently, Crk-III which comprises 283 amino acids was reported.

Pseudogene

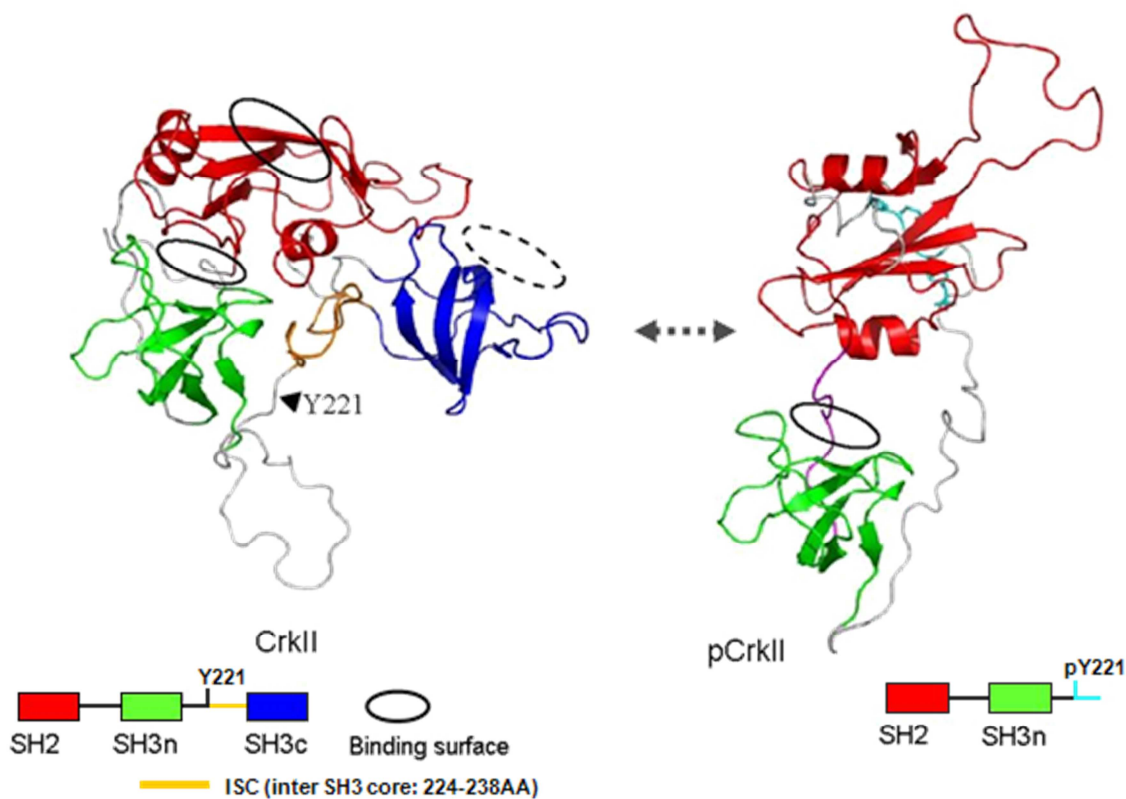
Not identified.



Crk-II gene comprises of three exons spanning on chromosome 17p13.3.



Tyrosine Y221 (human) of CrkII can be tyrosine phosphorylated and SH2 domain of CrkII binds to pY221 intramolecularly.



Structure of signaling adaptor protein CrkII. Adapted from Kobashigawa et al. (2007).

Protein

Note

Crk was originally isolated as avian retrovirus (CT10, chicken tumor No. 10) encoding oncoprotein as v-Crk (viral Crk, CT10 regulator of kinase).

Crk-II is composed of SH2-SH3(N)-SH3(C) and alternative splicing product Crk-I which deleted SH3(C) as SH2-SH3(N).

Description

NMR analysis of Crk-I, Crk-II, and phosphorylated form of Crk-II (aa 1-231). Crk-I has flexible structure of the linker region, thus individual SH2 or SH3

domain freely access to the targets (data not shown). Unphosphorylated form of Crk-II exhibits compact structure, and each SH domains were relatively fixed around inter SH3 region (designated as ISC: inter SH3 core; yellow in the figure below).

In this form, interaction surface of SH3(N) is in the semi-closed status. Upon tyrosine phosphorylation of Y221, SH2 binds to pY221 and structure is dramatically altered and SH3(N) surface is completely blocked by internal structure. Thus, pCrk-II is signaling-OFF form.

Expression

Ubiquitous.

Localisation

Mostly cytoplasm.

Function

Signaling adaptor protein which links tyrosine kinases and small G proteins.

Crk transmits signals from extracellular stimuli such as growth factors and extracellular matrices. SH2 domain of Crk bound to tyrosine phosphorylated peptide motif as YXXP. In focal adhesion complex, Crk binds to p130Cas which

possesses six Crk binding consensus sequences and to paxillin. Crk activates Fak and transmit signals to PI3 kinase.

Crk also binds to growth factor receptors such as EGFR or FGF, in addition to downstream signaling scaffold protein Gab1 which is mainly activated by HGF.

CRK transmits signals to small G proteins through its SH3 domain binding target C3G and DOCK180 those can activate Rap/R-Ras and Rac, respectively, and regulates cell growth, adhesion, and motility.

Crk plays various roles including cell growth, differentiation, phagocytosis, glucose transport, and infectious diseases.

Homology

CrkL (Crk-like).

Implicated in

Various diseases

Note

Crk is overexpressed in various human cancers especially in lung adenocarcinoma and in brain tumor.

Crk knockdown study demonstrates the essential roles for Crk in malignant potentials of various human cancers including ovarian cancer, sarcoma, and brain tumor.

Recently, microRNA-126 was shown to suppress lung cancer growth by the suppression of Crk expression. Crk has been reported to bind to NS1 protein of influenza virus type H5N1, CagA protein of *Helicobacter pylori*, and also known to regulate the infection of *Pseudomonas aeruginosa* and *Shigella flexneri*.

Therefore, Crk can be a therapeutic target molecule for cancer and infectious diseases.

Lung cancer

Note

96 cases of lung adenocarcinoma were analyzed by using Gene chip and in the cases of stage III, mRNA levels of Crk were increased comparing to those of in stage I (Beer et al., 2002).

Affymetrix oligonucleotide arrays were used to analyze 86 lung adenocarcinomas and 10 uninvolved lung tissues, and Crk mRNA expression was increased in more advanced (stage III versus stage I), larger (T2-4 versus T1), and poorly differentiated tumors and in

tumors from patients demonstrating poor survival (Miller et al., 2003).

Immunohistochemical analysis of Crk-II demonstrated that the levels of Crk-II were significantly elevated in most of the tumors, particularly in the colon and lung cancers. Furthermore, immunoblot analysis using human lung cancer cell lines revealed that the expression levels of Crk-II were correlated to growth rates of cells (Nishihara et al., 2002).

Prognosis

Expression of Crk mRNA was increased in patients with poor prognosis ($P=0.00034$) (Miller et al., 2003).

Brain tumor

Note

CrkII mRNA was detected both in normal brain and glioblastoma tissues, whereas crkI mRNA levels were quite low in normal brain and up-regulated in glioblastoma tissues.

Expression of CrkI but not CrkII in glioblastoma U87MG cells induced transformation that stimulated cell migration and invasion concomitant with tyrosine phosphorylation of p130 Cas (Takino et al., 2003).

Crk-knockdown cell lines of glioblastoma KMG4 was established by siRNA, and early phase of cell adhesion to laminin was found to be suppressed. Wound healing assay revealed the decreased cell motility in Crk knockdown cells, and suppression of both anchorage-dependent and -independent growth were demonstrated in these cells. Furthermore, in vivo tumor forming potential was also markedly suppressed (Wang et al., 2007).

Ovarian cancer

Note

Crk expression was targeted in the human ovarian cancer cell line MCAS through RNA interference, resulting in disorganized actin fibers, reduced number of focal adhesions, and decreased Rac activity in association with suppression of cell motility and invasion, and anchorage-dependent growth in soft agar. Tumor forming potential in nude mice was attenuated and intraperitoneal dissemination was not observed when Crk knockdown cells were injected into the peritoneal cavity (Linghu et al., 2006).

Breast cancer

Note

CrkI/II knockdown resulted in a significant decrease in migration and invasion of multiple malignant breast and other human cancer cell lines (MDA-231, MDA-435s, H1299, KB, and HeLa). Moreover, CrkI/II knockdown decreased cell spreading on extracellular matrix and led to a decrease in actin stress fibers and the formation of mature focal adhesions.

Using immunohistochemistry, we show elevated CrkI/II protein levels in patients with breast adenocarcinoma (Rodrigues et al., 2005).

Synovial sarcoma

Note

Crk adaptor protein is required for the sustained phosphorylation of Gab1 in response to HGF, leading to the enhanced cell motility of human synovial sarcoma cell lines SYO-1, HS-SY-II, and Fuji. Crk knockdown by RNA interference disturbed this HGF-induced tyrosine phosphorylation of Gab1. The elimination of Crk in these cells induced the disorganization of actin cytoskeleton and complete abolishment of HGF-mediated Rac1 activation and cell motility. Furthermore, the depletion of Crk remarkably inhibited the tumor formation and its invasive growth *in vivo* (Watanabe et al., 2006).

Oral cancer

Note

The expression of CRKII in 71 primary oral squamous cell carcinomas and 10 normal oral mucosal specimens was determined immunohistochemically, and the correlation of CRKII overexpression with clinicopathological factors was evaluated. Overexpression of CRKII was detected in 41 of 70 oral squamous cell carcinomas, the frequency being more significant than in normal oral mucosa. In addition, CRKII overexpression was more frequent in higher-grade cancers according to the T classification, N classification, and invasive pattern. Moreover, RNAi-mediated suppression of CRKII expression reduced the migration and invasion potential of an oral squamous cell carcinoma cell line, OSC20 (Yamada et al., 2011).

Endometriosis

Note

The expression levels of miR-126 and its putative target Crk mRNA were quantified using real time PCR in ectopic endometrium and eutopic endometrium in patients with endometriosis. The expression level of miR-126 was significantly downregulated in ectopic endometrium whereas the protein levels of Crk was increased. Thus, miR-126 may play an initial role in the development and progression of endometriosis (Liu et al., 2012).

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This article should be referenced as such:

Tanaka S. CRK (v-crK sarcoma virus CT10 oncogene homolog (avian)). *Atlas Genet Cytogenet Oncol Haematol*. 2012; 16(8):521-525.
