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Gene Section
Mini Review

KIAA1524

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Identity

Other names: CIP2A; FLJ12850; MGC163436; p90

HGNC (Hugo): KIAA1524

Location: 3q13.13

DNA/RNA

Description

The gene spans 38.8 kb and consists of 21 exons.

Transcription

3.3 kb mRNA. Alternate splicing: there are predicted splice variants, but none of them are experimentally verified.

Protein

Description

Translation: 905 amino acids.
Family: not defined.

Expression

Increased expression of CIP2A/KIAA1524 has been observed in various highly proliferating cancer cells. CIP2A is overexpressed in several types of human cancer tissues (gastric, breast, colon, squamous cell carcinomas of head and neck). Low expression of CIP2A/KIAA1524 is seen in most of the normal tissues, except in testis. CIP2A mRNA and protein expression is positively regulated by oncoprotein MYC whereas no change is seen in CIP2A expression in response to serum stimulation or during the cell cycle. A recent study demonstrated that Helicobacter pylori CagA-induced CIP2A expression is dependent on Src and MEK/ERK pathways.

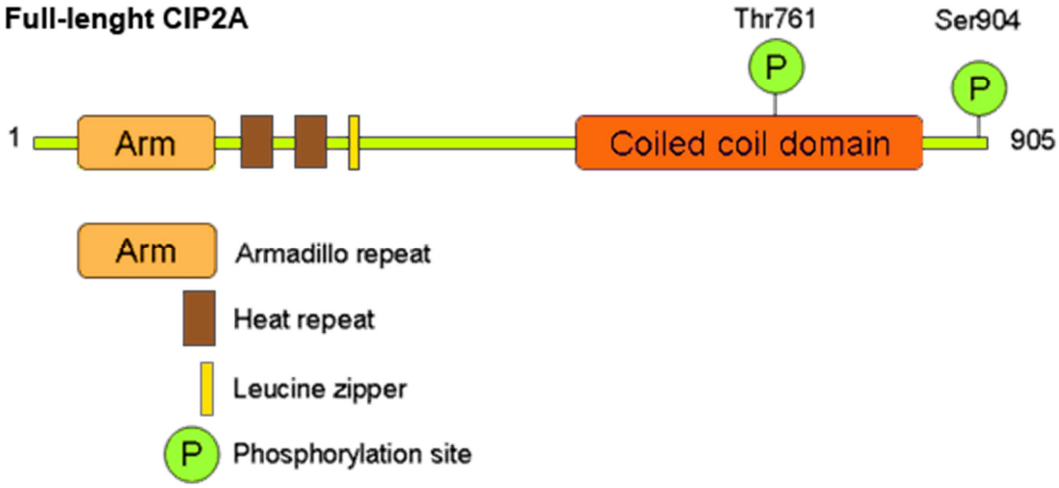
Localisation

Cytoplasmic and perinuclear region.

Function

Human oncoprotein. Interacts with Protein Phosphatase 2A (PP2A) and inhibits PP2A-mediated dephosphorylation and subsequent proteolytic degradation of MYC protein. Inhibition of CIP2A expression by siRNA inhibits anchorage-independent growth of several types of human cancer cells. CIP2A inhibition also prevents tumor growth in mouse xenograft models. Two studies have shown that CIP2A siRNA induces expression of acidic b-galactoside indicating induction of cellular senescence.

Structure of CIP2A gene.



Predicted modular structure of CIP2A. The indicated areas represent Armadillo repeats (Arm), leucine zipper (LZ) and coiled coil region. This prediction is based on programs superfamily 1.73 (Arm repeats), Prosite freq pat (leucine zipper) and Smart (coiled coil region). The phosphorylation sites have been identified in Daub et al., (2008) Mol Cell 31, 438-448, and the Ser904 has been reported also in Beausoleil et al., (2006) Nat Biotechnol 24, 1285-1292. Both studies analyzed peptides by mass spectrometry in high-throughput manner.

Homology

CIP2A is well-conserved among mammalian species, sharing more than 90% identity. Vertebrates like Xenopus laevis (frog) and Danio rerio (bony fish) have homologs with 65% and 50% identity with human CIP2A respectively. Lower conservation of Cip2A is found throughout the animal kingdom. Nematostella vectensis (starfish) has a Cip2A homolog that has 39% identity with the human protein, but contains several deletions in the sequence, whereas Drosophila melanogaster (fly) homolog has a only 15% identity with human protein.

Implicated in

Gastric cancer

Note

Several studies have shown CIP2A to be overexpressed in gastric cancer patients and cell lines (Soo Hoo et al., 2002; Li et al., 2008; Khanna et al., 2009). Furthermore, CIP2A depletion is shown to decrease proliferation, anchorage-independent growth, and expression of c-MYC protein in several gastric cancer cell lines (Khanna et al., 2009). CIP2A depletion also causes diminished clonogenic potential of tumor cells as well as induction of senescence in few gastric cancer cell lines (Li et al., 2008). Additionally, CIP2A and c-MYC immunopositivity associate in human gastric cancer specimens (Khanna et al., 2009).

Prognosis

Overexpression of CIP2A is associated with reduced overall survival in gastric cancer patients with tumour ≤ 5 cm, advanced stage (pT3-T4), and p53 immunopositivity. Moreover, association between CIP2A and markers of increased cellular malignancy (high SPF) further supports the role for CIP2A in promoting cancer progression (Khanna et al., 2009).

Colon carcinoma

Note

CIP2A mRNA expression is shown to be overexpressed in colon cancer tissues compared to non-malignant tissue (Junttila et al., 2007).

Head and neck squamous cell carcinoma (HNSCC)

Note

CIP2A mRNA and protein expression is shown to be overexpressed in human HNSCC cell lines. CIP2A immunopositivity in HNSCC tumor samples is restricted to tumour cells as stroma is mostly shown to be negative. Moreover, CIP2A is shown to promote c-MYC stability and malignant growth in NSCC cells.
Additionally, role of CIP2A expression in HNSCC is analyzed using a mouse model of HNSCC wherein strong CIP2A immunopositivity is shown in both hyperplastic and HNSCC tissues in comparison to DMBA treated wild type mice (Junttila et al., 2007).

Breast carcinoma

Note

CIP2A mRNA is not only shown to be overexpressed but also correlates with higher Scarff-Bloom-Richardson grades in samples from two independent human breast cancer patient cohorts. Furthermore, CIP2A mRNA expression positively correlated with lymph node positivity, expression of proliferations markers (Ki67) and p53 mutations in the tumor samples. Moreover, CIP2A protein expression was induced in mouse breast cancer mouse models presenting mammary gland-specific depletion of p53

and either BRCA1 or BRCA2. CIP2A depletion inhibits the expression of c-MYC, and anchorage-independent growth in breast cancer cells. Additionally, CIP2A is shown to support MDA-MB-231 xenograft growth in nude mice (Côme et al., 2009).

Helicobacter pylori (H. pylori) infection

Note

H. pylori infection-induced CIP2A expression in cultured cells is dependent on CagA gene expression and CagA phosphorylation. Bacterial oncoprotein, CagA upregulates CIP2A expression and this upregulation is dependent on Src and MEK/ERK pathways. H. pylori infection-induced MYC stabilization is also shown to be partially reduced on CIP2A depletion (Zhao et al., 2009).

To be noted

Other oncogenic properties of CIP2A: CIP2A is shown to promote Ras-elicited foci formation in mouse embryo fibroblasts and transforms immortalized human cells (HEK-TERV) (Junttila et al., 2007).

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