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Gene Section
Review

CCNA1 (cyclin A1)

Immacolata Vocca, Gianmarco Muzi, Francesca Pentimalli, Antonio Giordano

INT-CROM, National Cancer Institute, 'Pascale Foundation', - Cancer Research Center, Via Ammiraglio Bianco 83013, Mercogliano, Avellino, Italy (IV, FP), Department of Human Pathology and Oncology, University of Siena, Siena, Italy (GM), INT-CROM, National Cancer Institute, 'Pascale Foundation', - Cancer Research Center, Via Ammiraglio Bianco 83013, Mercogliano, Avellino, Italy; Department of Human Pathology and Oncology, University of Siena, Siena, Italy; Sbarro Institute for Cancer Research and Molecular Medicine, College of Science and Technology, Temple University Philadelphia, PA, USA (AG)

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Identity

HGNC (Hugo): CCNA1

Location: 13q13.3

DNA/RNA

Description

The CCNA1 gene is located at chromosome 13q12.3-q13 (Yang et al., 1997) and made up of 9 exons and 8 introns that extend over ~ 13 kb (Müller et al., 1999).

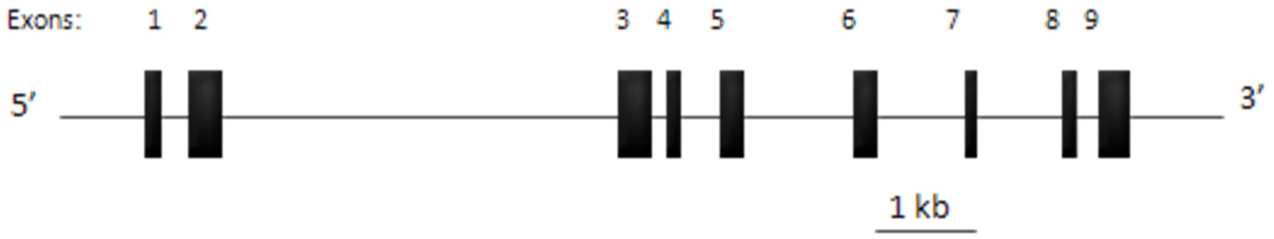
Transcription

2,1 kb mRNA; coding region is from 130 to 1527 bp (Yang et al., 1997). The cyclin A1 promoter does not possess a TATA box, whereas the region upstream of the transcriptional start site region contains four GC boxes, with multiple Sp1-binding sites important for the regulation of cyclin A1 expression (Müller et al., 1999).

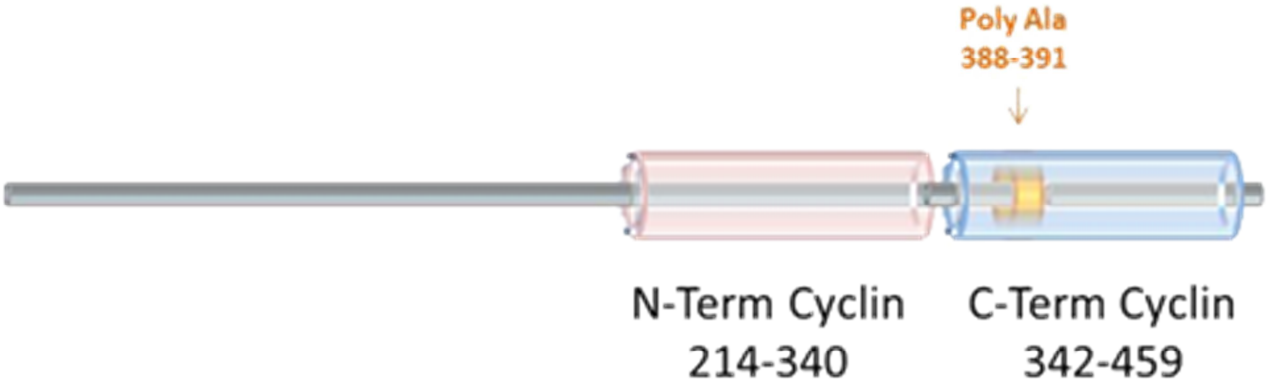
Three different transcript variants exist: isoform "a" is the longest transcript and encodes the longest isoform; isoform "b" has an alternate in-frame splice site in the 5' coding region resulting in a protein that is 1 amino acid shorter than isoform "a"; isoform "c" contains a distinct 5' UTR and lacks an in-frame portion of the 5' coding region, resulting in a 44 aa shorter N-terminus compared to isoform "a".

Pseudogene

None described.



Exons are represented by solid dark rectangles.



Schematic diagram of human cyclin A1. The positions of the cyclin box (with the two cyclin box folds) and the polyalanine sequence are shown. Numbers represent the amino acids positions.

Protein

Description

MW: 52 kDa. Amino acids (aa): 465 full-length isoform a (464 aa isoform b; 421 aa isoform c). Cyclin A1 is a member of the highly conserved cyclin family whose members are able to control the progression of cells through the cell cycle by activating cyclin-dependent kinases (CDKs). Within the protein the cyclin box is a region of protein sequence homology that is common to all members of the cyclin family and is required for interaction with the CDK partner.

Expression

Cyclin A1 expression is tissue-specific and high levels of expression are restricted to testis; a lower expression is reported in other human cell lines and in healthy brain. Cyclin A1 is also expressed in several myeloid leukemia cell lines and various other tumour types (Yang et al., 1997; Wegiel et al., 2008). Cyclin A1 is expressed at low levels in G0 phase and increases in early G1, S and G2/M phases (Yang et al., 1997; Yang et al., 1999).

Localisation

Mammalian cyclin A1 is primarily localized in the nuclei of spermatocytes in mouse and human (Liu et al., 1998; Liao et al., 2004). Cyclin A1 has an important role in the development of acute myeloid leukemia (AML): its localization in normal hematopoietic cells is nuclear, whereas in leukemic cells from AML patients and cell lines, it is predominantly cytoplasmic (Ekberg et al., 2004).

Function

Cyclin A1 belongs to the A-type cyclin family of proteins originally identified as 60 kDa polypeptides associated to CDK2 and interacting with viral proteins (Giordano et al., 1989; Giordano et al., 1991). Cyclin A family members are characterized by a typical periodicity in protein abundance through the cell division cycle functioning as activating subunits of enzymatic complexes, together with cyclin-dependent kinases (CDKs) (Lapenna and Giordano, 2009).
Cyclin A2, also known as cyclin A, is the major A-type cyclin in mammals. Cyclin A1 primarily functions in the meiotic cell cycle, but it also seems to contribute to G1/S cell cycle progression in somatic cells (Ji et al., 2005). Human cyclin A1 interacts with CDK2 in vitro and in vivo (Yang et al., 1997) and the resulting complex is essential for spermatogenesis and contributes to leukemogenesis, although its molecular functions remain largely unclear. Male knockout mice lacking cyclin A1 are infertile owing to a cell cycle arrest before the first meiotic division (Liu et al., 1998). Cyclin A1 interacts also with E2F1 and the retinoblastoma protein (Yang et al., 1999), with GPS2 (Diederichs et al., 2004), binds to and activates B-MYB in leukemic blasts (Müller-Tidow et al., 2001). Moreover the cyclin A1-CDK2 complex regulates DNA double-strand break repair following radiation damage (Müller-Tidow et al., 2004) by competing with CDK2-cyclin A2 for the binding to Ku70, a pivotal player in the non-homologous end-joining double strand break repair pathway, and inhibiting apoptosis through modulating RB functions in leukemia cells (Ji et al., 2007). Consistently, cyclin A1 knockout mice and Xenopus embryos show defects in the DNA repair process and are more prone to undergo apoptosis (Müller-Tidow et al., 2004; Cho et al., 2006). Finally, following exposure to DNA damaging agents, cyclin A1 is strongly upregulated and localizes to the nucleus. Inhibition of this upregulation, through roscovitine treatment, resulted in a significant decrease of DNA repair and an increase of DNA damage over time (Federico et al., 2010).

Homology

The percentage of identity below represents identity over an aligned protein region using pairwise alignment function of ClustalW software:
Bos taurus: 87%
Rattus norvegicus: 85%
Mus musculus: 84%

Xenopus tropicalis: 60%
Xenopus laevis: 59%
Danio rerio: 53%

Mutations

Germinal

None.

Somatic

Some mutations in the CCNA1 gene have been found in several tumor types. No insertions, nonsense substitutions or deletions have been described, whereas, some substitutions leading to missense (P50L in skin; A429V in stomach; C452Y in ovary) or silent mutations (Y107Y in stomach; L122L in lung; A391A in ovary) have been reported and were obtained from the Sanger Institute Catalogue Of Somatic Mutations In Cancer web site (Bamford et al., 2004).

Implicated in

Leukemias

Note

Cyclin A1 is expressed in the majority of myeloid and undifferentiated hematological malignancies as well as in normal hematopoietic progenitor cells (Krämer et al., 1998).

It has an important role in the development of acute myeloid leukemia (AML): overexpression of murine cyclin A1 in the myeloid lineage of transgenic mice leads to abnormal myelopoiesis in the first months after birth and to the development of AML at a low frequency over the course of 7-14 months.

This indicates that cyclin A1 overexpression results in abnormal myelopoiesis and is necessary to induce transformation thus contributing to leukemogenesis (Liao et al., 2001). Cyclin A1 expression is an independent prognostic factor in predicting overall survival and disease-free survival in AML patients (Ekberg et al., 2005) and high expression levels of both cyclin A2 and A1 are associated with good prognosis in the same patients (Nakamaki et al., 2003).

Its localization in normal hematopoietic cells is nuclear, whereas in leukemic cells from AML patients and cell lines, it is predominantly cytoplasmic (Ekberg et al., 2004). The frequency of cyclin A1 overexpression is also high in acute promyelocytic leukemia (APL) as a consequence of the APL-associated aberrant fusion proteins (PML-retinoic acid receptor alpha [PML-RAR alpha] or PLZF-RAR alpha) (Müller et al., 2000). Cyclin A1 is highly expressed in lymphoblastic leukemic cell lines and in childhood acute lymphoblastic leukemia (ALL) patients and its expression correlates with patient age and with a poorer event-free survival (Holm et al., 2006).

Interestingly, in human promyelocytic leukemia cells HL60, cyclin A1 expression is regulated by a miR34b-CREB axis, which seems to be crucial for myeloid transformation (Pigazzi et al., 2009).

Disease

AML is a relatively rare cancer of the myeloid line of blood cells, characterized by the rapid growth of abnormal white blood cells that accumulate in the bone marrow and do not mature, thereby interfering with the production of normal blood cells.

APL is a subtype of AML characterized by a chromosomal translocation involving the retinoic acid receptor alpha (RARα or RARA) gene and is unique, compared to other forms of AML, in its responsiveness to all trans retinoic acid (ATRA) therapy.

In ALL, malignant, immature white blood cells continuously multiply and are overproduced in the bone marrow. ALL causes damage and death by crowding out normal cells in the bone marrow, and by spreading to other organs.

Prostate cancer

Note

Cyclin A1 promotes cell survival in response to growth factors through PI3K/Akt signaling (Wegiel et al., 2008). Also, cyclin A1 mediates VEGF expression in cooperation with Rb- and androgen-dependent pathways (Wegiel et al., 2005). In particular, cyclin A1, by interacting with AR, binds to VEGF and MMP2 promoters and increases their expression, thus contributing to prostate cancer invasion (Wegiel et al., 2008).

Disease

Prostate cancer is a slow-growing cancer that develops in the prostate.

Cancer cells can metastasize from the prostate to secondary sites, particularly the bones and lymph nodes.

Treatment options are primarily surgery, radiation therapy, stereotactic radiosurgery and proton therapy.

Prognosis

Many prostate cancers are successfully cured and most patients will ultimately die from causes other than the disease itself.

Testicular cancer

Note

Cyclin A1 is highly expressed in aggressive testicular germ cell tumors (Müller-Tidow et al., 2003).

Among the different histological subtypes of testicular tumors, embryonal cell carcinomas and immature teratomas expressed the highest levels of cyclin A1, whereas intermediate levels were expressed in seminomas and yolk sac tumors. Cyclin A1 expression was very low in mature teratomas.

Disease

Testicular cancer is a common cancer in males that develops in testicles. If it is diagnosed early, in the great majority of cases it can be treated by surgery,

radiation and/or chemotherapy.

Cervical cancer

Note

Ectopic expression of miR-372 suppresses cell growth and induces arrest in the S/G_2 phases of cell cycle in HeLa cells by targeting CDK2 and cyclin A1 (Tian et al., 2011).

Also, it seems that in invasive cervical cancer the integrated form of HPV might affect CCNA1 promoter methylation (Yanatatsaneejit et al., 2011). In human cervical cancer cells, down-regulation of pSrcY416 inhibits cell proliferation by increasing the cell population in the G0-G1 phase and causes the up-regulation of p21Cip1 and p27Kip1 and the decrease of cyclin A1, cyclin E, and CDK-6, cyclin B and CDK-2 (Kong et al., 2011). Also, overexpressed Notch1 results in significant growth inhibition of human cervical carcinoma cells, which is related to a decrease of cyclin A1, cyclin E and pRb protein expression (Wang et al., 2007). The CCNA1 gene is never methylated in normal cervices and rarely in low-grade squamous intraepithelial lesions, whereas its methylation frequency increases with the severity of cervical lesions (Yang et al., 2010). In human papillomavirus-associated cervical cancer, promoter hypermethylation is also specific to the invasive phenotype in comparison with other histopathological stages during multistep carcinogenesis (Kitkumthorn et al., 2006).

Disease

Cervical cancer is a malignant neoplasm of the cervix. In almost all cases, human papillomavirus (HPV) infection is a necessary factor in the development of this cancer. Treatment includes surgery in early stages and chemotherapy and radiotherapy in advanced stages of the disease.

Prognosis

It is usually a slow-growing cancer, in some cases there might be no obvious symptoms until the cancer is in its advanced stages.

Head and neck squamous cell carcinoma (HNSCC)

Note

Methylation of CCNA1 is an important risk factors for HNSCC development since the cyclin A1 promoter is methylated in salivary rinses from HNSCC patients (Sun et al., 2012). The CCNA1 promoter is methylated in 45% of tumours but in none of the normal tissues and this methylation is inversely related to p53 mutational status in primary tumors (Tokumaru et al., 2004). In another study, cyclin A1 promoter methylation is associated with human papillomavirus 16 induced HNSCC, independently of p53 mutation (Weiss et al., 2011).

Disease

HNSCC refers to the squamous cell carcinomas of the oral cavity, pharynx and larynx. The major risk factor for head and neck cancer is chronic exposure of epithelia to tobacco smoke and alcohol, UV light, some chemicals and human papillomavirus.

Prognosis

HNSCC are frequently aggressive; patients are at a higher risk of developing another cancer in the head and neck area. These cancers are highly curable if detected early, surgery and radiotherapy are the main modality of treatment. Chemotherapy, acting as a radio-sensitizer, increases survival in locally advanced disease. Recently, inhibition of epidermal growth factor receptor (EGFR) has proved a successful therapeutic strategy.

Bladder cancer

Note

The CCNA1 promoter has been found hypermethylated in urine sediments from bladder cancer patients (Yu et al., 2007). Also, in another study, the CCNA1 gene displays high frequency of methylation in bladder cancer samples and no methylation in normal uroepithelium, indicating a potential role of cyclin A1 in the pathogenesis and spread of bladder cancer (Brait et al., 2008). Interestingly, the deubiquitinating enzyme USP2a can bind cyclin A1 and consequently blocks its ubiquitination and degradation. Enforced expression of USP2a resulted in cyclin A1 accumulation and increased cell proliferation in bladder cancer cells (Kim et al., 2012).

Disease

Bladder cancer is a cancer of the urothelium. Treatment options for people with bladder cancer are surgery, chemotherapy, biological therapy, and radiation therapy.

Breast cancer

Note

Six1 overexpression in mammary cells induces genomic instability and malignant transformation that is dependent on upregulation of its transcriptional target cyclin A1 (Coletta et al., 2004). Consistently, in another study, the tumor suppressor miR-185, by inhibiting the expression of Six1 and consequently of its transcriptional targets c-myc and Cyclin A1, sensitizes cancer cells to apoptosis (Imam et al., 2010). Also, in the malignant breast cancer cell line MDA-MB-231, the dysregulation of activating transcription factor-3 by TGFβ1 activates cyclin A1 and MMP-13 leading to cell invasion and metastasis (Kwok et al., 2009). The histone demethylase JMJD2B is regulated by both ERalpha and HIF-1alpha driving breast cancer cell proliferation in normoxia and hypoxia, and epigenetically regulates the expression of cell cycle genes such as CCND1, CCNA1, and WEE1 (Yang et al., 2010). On the contrary, the dietary supplement BreastDefend inhibits proliferation and invasive behavior of the highly metastatic MDA-MB-231 cell line by downregulating the expression of CCNA1 and

CDK6 genes (Jiang et al., 2011). Bisphenol A promotes mammary carcinogenesis by stimulating the DNA methylation of genes related to development of most or all tumor types, including the CCNA1 gene (Qin et al., 2012).

Disease

Breast cancer is a type of cancer originating from breast tissue. The size, stage, rate of growth and other characteristics of the tumor determine the kinds of treatment which may include surgery, hormonal, therapy and chemotherapy, radiation and/or immunotherapy.

Other cancers

Note

Some studies indicate a potential tumor suppressor role for cyclin A1 in nasopharyngeal carcinomas, colon carcinomas, oral carcinomas, melanomas, and hepatocellular carcinomas (Yanatatsaneejit et al., 2008; Xu et al., 2004; Shaw et al., 2006; Garrido et al., 2012; Yu et al., 2003). Also, Cyclin A1 mediates apoptosis, G2/M arrest, and mitotic catastrophe in renal, ovarian, and lung carcinoma cells through an inappropriate activation of CDK1 (Rivera et al., 2006). Other studies show that cyclin A1 is overexpressed in human hepatocellular carcinoma (Studach et al., 2012) and correlates with a poor outcome in ependymomas (Lukashova-v Zangen et al., 2007).

The information contained herein was partially compiled using Proteinquest, a software able to automatically parse the scientific literature to extract relevant data.

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