Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

ANXA1 (annexin A1)

Flavia Cristina Rodrigues-Lisoni, Tiago Henrique, Eloiza Helena Tajara

Department of Biology and Zootechny, Faculty of Engineering of Ilha Solteria (UNESP), Ilha Solteira, Brazil (FCRL); Department of Molecular Biology, School of Medicine (FAMERP), Sao Jose do Rio Preto, Brazil (TH, EHTDS)

Published in Atlas Database: May 2010

Online updated version: http://AtlasGeneticsOncology.org/Genes/ANXA1ID653ch9q21.html
DOI: 10.4267/2042/44953

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Identity

Other names: ANX1, LPC1

HGNC (Hugo): ANXA1

Location: 9q21.13

Local order: According to NCBI Map Viewer, genes flanking ANXA1 in centromere to telomere direction on 9q21 are: LOC100289351, RPS20P24, TMC1, RPS27AP15, ALDH1A1, LOC100133307, LOC100132782, ANXA1, LOC138971, LOC100130911, RORB, TRPM6, RNY4P1.

DNA/RNA

Description

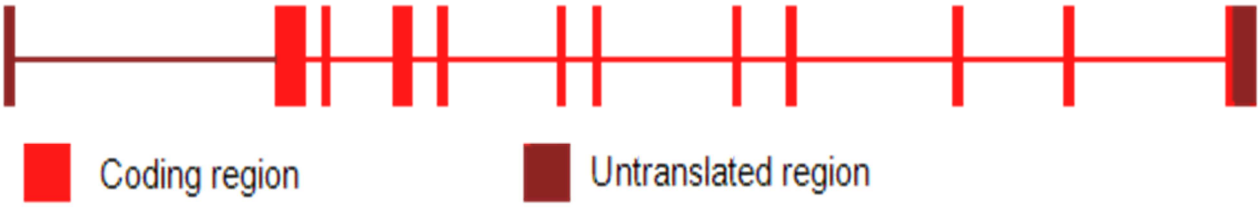
The exon-intron organization of ANXA1 genes in vertebrates have been described and are highly conserved, each gene consisting of 13 exons of which the first and last are uncoding 5' and 3' sequences, with the translation initiator codon (AUG) found near the beginning of the second exon (Kovacic et al., 1991).

Transcription

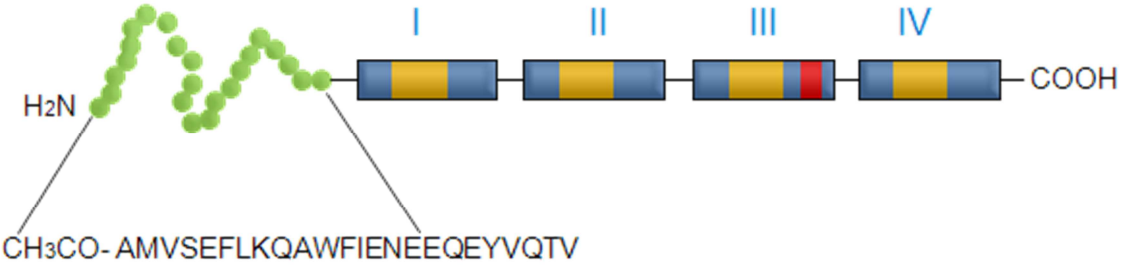
Transcription produces 9 different mRNAs to this gene. The ANXA1 gene is expressed in the tissues: bone, bone marrow, brain, cartilage, cerebellum, cerebrum, cervix, colon, ear, embryonic tissue, endocrine, esophagus, eye, fetus, gastrointestinal tract, heart, kidney, liver, lung, lymph node, lymphoreticular, mammary gland, muscle, nervous, ovary, pancreas, pancreatic islet, parathyroid, peripheral nervous system, pituitary gland, placenta, pooled tissue, prostate, salivary gland, skin, soft tissue, spleen, stem cell, stomach, synovium, t-cell, testis, thymus, thyroid, uncharacterized tissue, uterus, vascular.

Pseudogene

No known pseudogenes.



ANXA1 gene. The ANXA1 gene contains 13 exons, of which the first and last are uncoding 5' and 3' sequences (red regions), with the translation initiator codon (AUG) found near the beginning of the second exon (orange regions).



Schematic representation of annexin protein. N-terminal region with amino acids and four repetitions with 70-75 amino acids in C-terminal region.

Protein

Note
Belongs to the annexin family. Contains 4 annexin repeats.

Description

The ANXA1 gene encodes a 38.71 kDa protein. Similarly to other annexins, annexin A1 is characterized by a C-terminal homologous domain with 4 to 8 repeats of 70-75 aminoacids, responsible for calcium and phospholipid binding properties. The variable N-terminal region is unique in length and sequence and includes potential sites of phosphorylation, glycosylation and peptidase action (Gerke and Moss, 2002).

Expression

The human ANXA1 gene promoter contains consensus sequences for: glucocorticoids, AP-1 and NFIL-6. However the regulation from glucocorticoid (GC) appear to be dependent upon an activation involving NFIL-6 or AP1 (Solito et al., 1998a; Solito et al., 1998b). The GC mediated regulations confirm the original studies which proposed ANXA1 as mediator of the glucocorticoid action (Flower, 1988). In mouse, in contrast, GC regulation is mediated through two consensus sequences present in the upstream region of TATA box (Horlick et al., 1991). However the data of Antonicelli et al. 2001 regarding sequences of the mouse Anxa1 promoter brought evidence of the involvement of the CREB transcription factor (the cyclic AMP-responding element-binding protein) in the activation of this gene by cyclic AMP and glucocorticoids.

Localisation

ANXA1 is preferentially localized in the cytoplasm and associated with the plasma membrane or cytoskeleton, but it has also been localized outside the plasma membrane.

Function

The function of the annexin A1 is far to be clear, it has been involved in signal transduction (Alldridge et al., 1999; de Coupade et al., 2000), vesicle transport (Diakonova et al., 1997), cell transformation (Violette et al., 1990; Solito et al.,
1998a), inflammation (Perretti and Gavins, 2003), cell matrix interaction and apoptosis (Raynal and Pollard, 1994; Solito et al., 2001; Solito et al., 2003).

Homology

The comparison of conserved and variable residues between human annexin 1 protein and annexin protein from different vertebrates shows amino acid identities of 100% (Pan troglodytes), 91% (Canis familiars), 87% (Mus musculus), 89% (Rattus norvegicus) and 77% (Gallus gallus) (Rodrigues-Lisoni et al., 2006).

Mutations

Note
Reduced expression of ANXA1 could be explain by some mechanisms include gene deletions and mutations, hyper-methylation of the promoter with subsequent loss of transcription, and alterations in the post-translation processing (e.g. phosphorylation) of the protein involved in annexins regulation (de Coupade et al., 2000; Rodrigues-Lisoni et al., 2006; Alves et al., 2008).
Lindgren et al. (2001) studied subjects with type 2 diabetes and find a G instead of T at nucleotide position 362 from the transcription start site (exon 5) of ANXA1 gene in all individuals sequenced.

Implicated in

Breast cancer

Disease
In breast cancer, ANXA1 is believed to function as a tumor suppressor. In study with a tissue microarray using 82 pairs of primary breast cancers and lymph node metastases from archival materials the results revealed that ANXA1 expression was lost in 79% of breast carcinomas, and there was no difference in ANXA1 expression between primary breast carcinoma and lymph node metastasis (Cao et al., 2008).

Prognosis
The suppressed ANXA1 expression in breast tissue is correlated with breast cancer development, progression and metastasis (Shen et al., 2006; Wang et al., 2010).

Oral squamous cell carcinoma (OSCC)

Disease

ANXA1 expression could be used as a suitable biomarker for patients with oral cavity cancer and its adoption for complementary non-invasive diagnosis of oral squamous cell carcinoma is suggested. Beyond the anti-inflammatory function, annexin A1 may also play a tumor suppressor role in peripheral blood cells (Faria et al., 2010).

Prognosis

The nuclear localization of ANXA1 protein is a frequent event and could be used as a prognostic factor in OSCC (Lin et al., 2008).

Laryngeal squamous cell carcinoma

Disease

In surgical tissue specimens from 20 patients with laryngeal squamous cell carcinoma, ultrastructural immunocytochemistry analysis showed in vivo down-regulation of ANXA1 expression in the tumor and increased in mast cells and laryngeal squamous carcinoma cell line treated with ANXA1 peptide. Combined in vivo and in vitro analysis demonstrated that ANXA1 plays a regulatory role in laryngeal cancer cell growth (Silistino-Souza et al., 2007).

Prognosis

ANXA1 dysregulation was observed early in laryngeal carcinogenesis, in intra-epithelial neoplasms (Alves et al., 2008).

Lung squamous cell carcinoma

Disease

The ANXA1 expression was identified by shot-gun proteomics strategy in lung squamous cell carcinoma.

Prognosis

The ANXA1 might play an important role in lung squamous cell carcinoma genesis, progression, recurrence, and metastasis and might be used as markers of this carcinoma (Nan et al., 2009).

Prostate cancer

Disease

The reduction of ANXA1 expression, commonly associated with prostate cancer, could be due to elevated activity of histone deacetylases (D'Acunto et al., 2010) and interleukin 6 expression (Inokuchi et al., 2009).

Prognosis

The ANXA1 expression is a contributing factor to the proapoptotic effects in prostate cancer (D'Acunto et al., 2010) and enhancing tumor aggressiveness via the upregulation of interleukin 6 expression and activity (Inokuchi et al., 2009).

Leukaemia

Disease

Immunocytochemical detection of ANXA1 represents a simple, inexpensive, highly sensitive and specific (100%) assay for diagnosis of hairy cell leukaemia. This assay will be especially useful in distinguishing hairy cell leukaemia from splenic lymphoma with villous lymphocytes and variant hairy cell leukaemia, both of which usually respond poorly to treatments that are effective in hairy cell leukaemia (Falini et al., 2004).

Prognosis

The downregulated ANXA1 expression contributes considerably to the drug resistance in leukemia cell line (Zhu et al., 2009).

Cervical cancer

Disease

A close association was observed between ANXA1 expression and tumour cell differentiation in invasive squamous cell carcinoma.

Prognosis

ANXA1 may be an effective candidate for detecting cervical intraephitelial neoplasia lesions and for evaluating tumour cell differentiation in squamous cell carcinoma of the cervix (Wang et al., 2008).

Gastric cancer

Disease

Loss of ANXA1 expression was significantly associated with advanced T stage, lymph node metastasis, advanced disease stage, and poor histological differentiation.

Prognosis

ANXA1 expression decreased significantly as gastric cancer progressed and metastasized, suggesting the importance of ANXA1 as a negative biomarker for gastric cancer development and progression (Yu et al., 2008).

Urinary bladder urothelial carcinoma

Disease

Comparative proteomics and immunohisto-chemistry demonstrated that ANXA1 is up-regulated in high grade urinary bladder urothelial carcinoma as compared to non-high grade carcinomas.

Prognosis

ANXA1 might be related to tumour progression. The ANXA1 overexpression and histological grade predicted disease-specific survival and metastasis-free survival (Li et al., 2010).

Systemic lupus erythematosus

Disease

Auto-antibodies against annexin A1 have been detected in patients with auto-immune diseases such as systemic lupus erythematosus (Hirata et al., 1981; Goulding et al., 1989).

Rheumatoid arthritis

Disease

ANXA1 has been recently shown to play a key role in T-cell activation and to be highly expressed in T cells from rheumatoid arthritis patients. Treatment of rheumatoid arthritis patients with steroid decreased ANXA1 expression in T cells.

Prognosis

Steroids regulate the adaptive immune response and suggest that ANXA1 may represent a target for the treatment of autoimmune diseases (D'Acquisto et al., 2008).

Crohn's disease

Disease

Corticosteroids are widely used to treat patients with inflammatory bowel disease although the response is variable. Corticosteroids mediate some of their actions through ANXA1, and the induction of autoantibodies to ANXA1 has been proposed as a possible mechanism by which steroid efficacy is suboptimal in vivo (Beattie et al., 1995).

Prognosis

The high levels of IgM ANXA1 antibodies in patients with Crohn's disease not taking corticosteroids provides further evidence of disturbed immunity in inflammatory bowel disease (Stevens et al., 1993).

Cystic fibrosis

Disease

Downregulation and degradation of ANXA1 was found in the bronchoalveolar lavage fluid of patients with cystic fibrosis indicating the susceptibility of these patients to lung inflammation. ANXA1 may be a key protein involved in cystic fibrosis pathogenesis especially in relation to the not well defined field of inflammation in cystic fibrosis (Tsao et al., 1998).

Prognosis

Decreased expression of annexin A1 contributes to the worsening of the cystic fibrosis phenotype (Bensalem et al., 2005).

Parkinson's disease

Disease

ANXA1 expression has been linked to Parkinson's disease. ANXA1 immunoreactivity has been found in ameboid microglia within the astrocytic envelope of neurons adjacent to or within glial scars in the parkinsonian substantia nigra (Knott et al., 2000).

Multiple sclerosis

Disease

ANXA1 expression has been identified in the lesions of multiple sclerosis plaque and correlated with the degree of the disease (Probst-Cousin et al., 2002).

Prognosis

Strategies aiming at reducing ANXA1 functions or expression in T cells might represent a novel therapeutic approach for multiple sclerosis (Paschalidis et al., 2009).

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This article should be referenced as such:

Rodrigues-Lisoni FC, Henrique T, Tajara EH. ANXA1 (annexin A1). Atlas Genet Cytogenet Oncol Haematol. 2011; 15(2):117-121.