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Review

ANKHD1 (ankyrin repeat and KH domain containing 1)

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Abstract

ANKHD1 is differentially expressed in human cancers, and potentially regulates multiple cellular functions and participates as a scaffold for protein-protein interactions through its ankyrin-repeat domains. Recently, studies have indicated that ANKHD1 is involved in the regulation of important biological process that participate in the malignant phenotype, including cell cycle progression, proliferation, clonogenicity and migration. The present review on ANKHD1 contains data on DNA/RNA, protein encoded and where the gene is implicated.

Keywords

ANKHD1; Cell cycle; Cell proliferation; Migration; Cancer

Identity

Other names: MASK, VBARP, PP2500

HGNC (Hugo): ANKHD1

Location: 5q31.3

DNA/RNA

Description

The entire ANKHD1 gene is about 147 Kb (start: 139781399 and end: 139929163 bp; orientation: plus strand). The ANKHD1 gene encodes for 4 transcript variants. The transcript variant 1 (start: 139781399 and end: 139919441 bp; orientation: plus strand; 34 exons; mRNA: 8233 bp) is the longest transcript and encodes the isoform 1 (2542 aa protein). The transcript variant 2 (start: 139781399 and end: 139852062 bp; orientation: plus strand; 11 exons; mRNA: 2161 bp) uses an alternate in-frame splice site in the 5` coding region, lacks several exons, uses an alternate 3` terminal exon and encodes the isoform 2, which is shorter and presents a distinct C-terminus compared to isoform 1 (616 aa protein). Transcript variant 3 (start: 139781399 and end: 139852062 bp; orientation: plus strand; 11 exons; mRNA: 2194 bp) lacks several exons, uses an alternate 3` terminal exon and encodes the isoform 3 that also has a distinct C-terminus compared to isoform 1 (627 aa protein). Transcrit variant 4 (start: 139781399 and end: 139852062 bp; orientation: plus strand; 10 exons, mRNA: 2084 bp) also lacks several exons, uses an alternate 3` terminal exon, encodes the isoform 4 that has a distinct C-terminus compared to isoform 1 and is the shortest of all isoforms (581 aa protein). Additionally, ANKHD1-EIF4EBP3 is a readthrough transcript involving ANKHD1 and EIF4EBP3 genes, which encodes a protein that contains multiple ankyrin repeats, single KH-domain and a C-terminus with a portion from the EIF4EBP3 gene (start: 139781399 and end: 139929163 bp; orientation: plus strand; 36 exons, mRNA: 8349 bp; protein: 2617 aa). Data searched at GenBank NCBI (http://www.ncbi.nlm.nih.gov/genbank/) and UCSC Genome Browser (https://genome.ucsc.edu/).

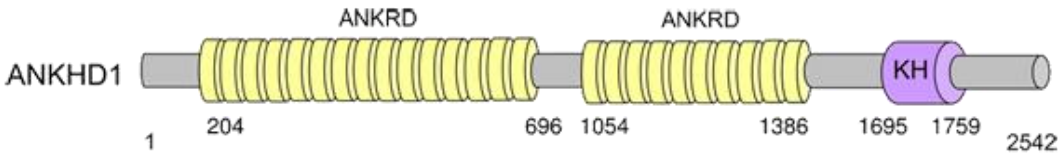

Figure 1. Schematic primary structure of ANKHD1 protein (isoform 1). Ankyrin repeat domains (ANKRD) and K homology (KH) domain are illustrated. The position of amino acids (aa) are indicated in the figure.

Protein

Description

The ANKHD1 protein has 4 isoforms. Isoforms 2, 3 and 4 are smaller and less characterized than isoform 1. Isoform 1 of ANKHD1 protein consists of 2542 amino acids with a molecular weight of 270 kDa, has 20 ankyrin repeats distributed in two blocks and a K homology (KH) domain in the C-terminal region. The schematic representation of ANKHD1 protein (isoform 1) is illustrated in Figure 1.

Expression

Ubiquitous.

Localisation

ANKHD1 is predominantly found in the cytoplasm (Figure 2).

Function

The ANKHD1 protein contains 20 ankyrin repeats, which are highly conserved structures. The presence of ankyrin repeats domains suggests that this protein integrates multiple signaling pathways and participates as scaffold for protein-protein interactions (Jernigan and Bordenstein, 2015). A large part of the knowledge regarding the functions of ANKHD1 was obtained by experiments using its orthologous protein Mask (multiple ankyrin repeats single KH domain). In Drosophila, Mask acts in the signal transduction pathway mediated by Cws (Corkscrew; orthologous of SHP2) (Smith, et al., 2002), participates in the Hippo signaling pathway activation through its association with Yki (Yorkie, orthologous of YAP1) (Sidor, et al., 2013, Sansores-Garcia, et al., 2013) and potentially regulates Hop signaling pathway (Hopscotch, orthologous of JAK) (Muller, et al., 2005).

In humans, ANKHD1 associates with SHP2, however the biologic consequence of this protein interaction remains indeterminate (Traina, et al., 2006). ANKHD1 and YAP1 interaction has also been confirmed in human cells (HEK293 and DU145 cells) and modulates the Hippo signaling pathway activation, proliferation and cell cycle progression (Sidor, et al., 2013, Sansores-Garcia, et al., 2013, Machado-Neto, et al., 2014).

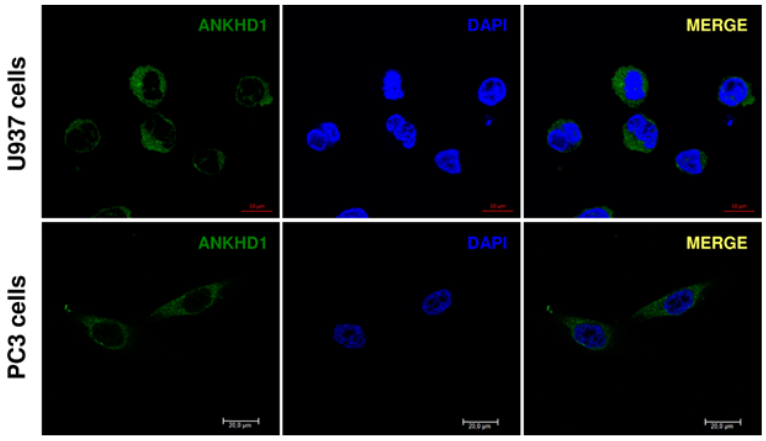

Figure 2. Intracellular localization of ANKHD1 protein in U937 and PC3 cells. Confocal analysis of U937 (leukemia) and PC3 (prostate cancer) cells displaying ANKHD1 (green) and DAPI (blue) staining; MERGE shows the overlapped images. Scale bar: 10 or 20 µm, as indicated. Note the predominant cytoplasm localization of ANKHD1. Anti-ANKHD1 (sc-160960) was from Santa Cruz Biotechnology and DAPI (P-36931) was from Life Technologies (Carlsbad, CA, USA). Personal data.

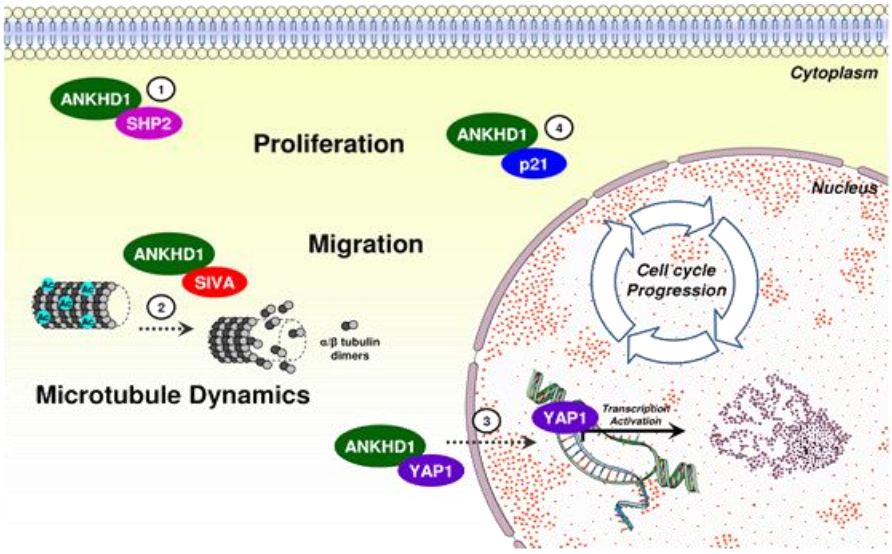

Figure 3. A potential model for ANKHD1 cellular functions and protein interactions. (1) ANKHD1 associates with SHP2, however the cell process involved in this protein interaction remains poorly understood. **(2)** ANKHD1 interacts to and modulates SIVA ability to regulate microtubule dynamics and migration. **(3)** ANKHD1 binds to and modulates the expression and activity of the co-activator transcription YAP1, **(4)** ANKHD1 modulates the expression of the cyclin-dependent kinase inhibitor p21, regulating cell cycle progression and proliferation. Abbreviations: Ac, acetylation. Figure was produced using Servier Medical Art (http://www.servier.com/Powerpoint-image-bank).

ANKHD1 interacts with SIVA and modulates the microtubule dynamics, cell proliferation and migration of human leukemia cells (Machado-Neto, et al., 2015). In addition, ANKHD1 modulates p21 (CDKN1A) expression and cell cycle progression in multiple myeloma cells (Dhyani, et al., 2015, Dhyani, et al., 2012). In NT2 cells, inhibition of the small isoform of ANKHD1 that lacks the KH domain (also designed as VBARP; isoform 3) triggered caspase-3/7 activation (Miles, et al., 2005), however no similar effect on apoptosis was observed in the other cell lines inhibited for all other ANKHD1 isoforms (Machado-Neto, et al., 2014, Machado-Neto, et al., 2015, Dhyani, et al., 2012). A potential model for ANKHD1 cellular functions and protein interactions is summarized in Figure 3.

Homology

ANKHD1 shares high homology with ANKRD17 (ankyrin repeat domain 17), both orthologous proteins to Mask protein from Drosophila. ANKHD1 also shares high homology among different species (Table 1).

Mutations

Somatic

Recurrent mutations in the ANKHD1 gene are rare, 180 substitution missense, 13 substitution nonsense, 58 substitution synonymous, 1 insertion frameshift and 1 deletion frameshift mutations are reported in COSMIC (Catalogue of somatic mutations in cancer; http://cancer.sanger.ac.uk/cancergenome/projects/cosmic).

Implicated in

Leukemia

Note

ANKHD1 was reported as highly expressed in leukemia cell lines and in primary bone marrow samples from patients with acute myeloid leukemia and acute lymphoid leukemia (Traina, et al., 2006). Interestingly, ANKHD1 silencing reduced cell proliferation, clonogenicity, migration and tumorigenesis of leukemia cells (Machado-Neto, et al., 2015).

Multiple myeloma

Disease

Multiple myeloma cell lines and primary plasma cells from myeloma multiple patients presented a high expression of ANKHD1 (Dhyani, et al., 2012). In multiple myeloma cell lines, ANKHD1 inhibition resulted in a delay in cell cycle progression and lower cell proliferation, clonal growth, migration and tumor formation (Dhyani, et al., 2015, Dhyani, et al., 2012).

% Identity for: *Homo sapiens* ANKHD1	Symbol	Protein	DNA
vs. M. mulatta	ANKHD1	99.1	99.8
vs. C. lupus	ANKHD1	97.2	94.3
vs. B. taurus	ANKHD1	96.6	93.8
vs. M. musculus	Ankhd1	92.6	90.0
vs. R. norvegicus	Ankhd1	92.6	89.8
vs. G. gallus	ANKHD1	87.2	81.5
vs. X. tropicalis	ankhd1	74.5	71.8
vs. D. rerio	ankhd1	74.9	66.7

Table 1. Comparative identity of human ANKHD1 with other species. (Source: http://www.ncbi.nlm.nih.gov/homologene)

Prostate cancer

Note

High expression of ANKHD1 was observed in prostate cancer cell lines (Machado-Neto, et al., 2014). Using the siRNA approach, ANKHD1 silencing reduced proliferation, tumor formation, and cell cycle progression in prostate cancer cells (Machado-Neto, et al., 2014).

Breast cancer

Prognosis

In two independent cohorts of breast cancer patients, high expression of ANKHD1 was associated with worsened outcomes (Sansores-Garcia, et al., 2013).

To be noted

Although ANKHD1 presents high homology with ANKRD17 (both orthologous proteins of Mask), the Ankrd17 knockout mice presents embryonic lethality (Hou, et al., 2009), indicating that these proteins do not play redundant functions. Another interesting point is that, accordingly to current data, ANKHD1 participates in cell proliferation and cell cycle progression in different neoplastic cells; however the ANKHD1-interacting proteins appear to vary, depending on the cellular context.

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