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Gene Section
Review

EYA2 (EYA transcriptional coactivator and phosphatase 2)

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Abstract

EYA2 encodes a co-activator for the SIX family of homeobox transcription factors. The SIX/EYA transcriptional complex plays important roles in organogenesis, promoting the proliferation and survival of progenitor cells. Abnormal re-expression of EYA2 in adult tissue promotes tumorigenesis and metastasis in multiple tumor types. In addition to its role as a co-activator, the EYA Domain (ED) of EYA2 contains a unique HAD family Tyr phosphatase activity, which plays a role in ERβ specific anti-tumor activity in breast cancer. The EYA2 Tyr phosphatase can also dephosphorylate H2AX, potentially playing a role in DNA damage repair. The N-terminal region of EYA2 also contains a Ser/Thr phosphatase activity, which may regulate the innate immune response.

Keywords: Transcriptional co-activator, phosphatase, organogenesis, oncogenesis.

Identity

Other names: EAB1

HGNC (Hugo): EYA2

Location : 20q13.12

DNA/RNA

Description

EYA2 gene is located at 20q13 (a frequently amplified region (Zhang et al., 2005)) and has 16 exons.

Transcription

The transcript of EYA2 gene is 2702 bp long. Coding sequence of EYA2 starts at the 375th bp and ends at the 1991st bp of the mRNA.

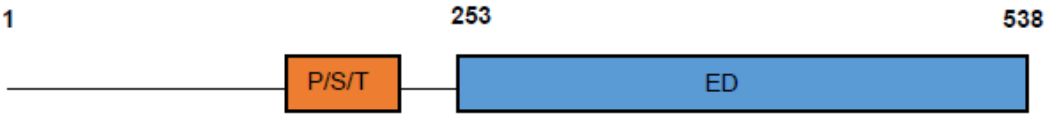
Pseudogene

No pseudogene has been reported for EYA2.

Protein

Description

The EYA2 gene encodes a 538 amino acid protein with a predicted molecular weight of 59 kDa.
It is composed of a flexible N-terminal region and a highly conserved C-terminal EYA domain (ED). The N-terminal region is poorly conserved among EYA family members (EYA1, EYA2, EYA3 and EYA4) and the lengths of the N-terminal region in EYA2 vary amongst species.
The N-terminal region contains a Pro/Ser/Thr rich transactivation domain that is responsible for activating SIX-mediated transcription (Xu et al., 1997a; Ohto et al., 1999).
The N-terminal region of all mouse EYA family members have been shown to possess Ser/Thr phosphatase activity, and this activity of EYA4 was shown to play a role in regulating the innate immune response (Okabe et al., 2009; Sano and Nagata, 2011).



A schematic representation of the EYA2 protein that contains a flexible N-terminal region and a highly conserved C-terminal EYA domain (ED).

The highly conserved C-terminal ED mediates the interaction between EYA2 and its protein partners, including SIX1 (Patrick et al., 2013). The ED of EYA2 also contains Mg^{2+}-dependent Tyr phosphatase activity (Krishnan et al., 2009; Yuan et al., 2014). Crystal structures of both the ED of human EYA2 and the SIX1/EYA2 ED complex have been determined, providing detailed structural information for the C-terminal half of EYA2 (Jung et al., 2010; Patrick et al., 2013).

Expression

To date, there has been no investigation of EYA2 protein levels in different developmental stages or tissues, but the mRNA transcripts of EYA2 have been examined by Northern blot, real time RT-PCR or in situ hybridization.

In general, EYA2 expression is high and widespread in embryo and is low and limited in adult tissues.

In situ hybridization in mouse embryo detected Eya2 in facioacoustic ganglionic complex, epibranchial placodes, nasal placodes, somites, branchial arch ectoderm, the trigeminal, dorsal root ganglia, cranial placodes, central nervous system, neural retina, sclera, optic nerve sheath (Xu et al., 1997b), and the tendons and ligaments of the limb (Xu et al., 1997a). EYA2 expression in limb displayed a pattern similar to that of SIX1.

In newborn mice, EYA2 was detected using Northern blot in the eye, brain, and lung at high levels, but was not detected in the skin, liver, intestine, and kidney (Duncan et al., 1997).

In adult mice, EYA2 mRNA remains at high levels in the eye lens, and is decreased in the lung and brain based on Northern blot analyses (Duncan et al., 1997). EYA2 mRNA can also be detected in thymus and uterus (Zimmerman et al., 1997).

In adult humans, EYA2 was predominantly observed in muscle, and at lower levels in kidney, placenta, brain, and pancreas based on Northern blot analyses (Duncan et al., 1997). RT-PCR revealed EYA2 mRNAs in human testis, colon, thymus, thyroid and prostate (Zhang et al., 2005).

Localisation

EYA2 is localized in both the nucleus and cytoplasm (Ohto et al., 1999; Fougerousse et al., 2002; Farabaugh et al., 2012). The SIX proteins actively translocate EYAs into the nucleus for SIX/EYA mediated transcriptional activation (Ohto et al., 1999).

Function

EYA2 functions both as a transcriptional co-activator and a protein phosphatase. Although EYA2 is best known for its role as a co-activator for the SIX family transcription factors, it can also form complexes with PAX6 (Xu et al., 1997b) and DACHSHUND (Heanue et al., 1999) to mediate transcriptional activation of downstream genes. SIX proteins promote cell proliferation and survival (Ford et al., 1998; Li et al., 2002; Li et al., 2003; Del Bene et al., 2004; Coletta et al., 2004; Zou et al., 2004; Zou et al., 2006), likely by collaborating with EYA proteins including EYA2. EYA2 is involved in the development of eye, kidney, ear, heart (Duncan et al., 1997), limb (Xu et al., 1997a), and cranial placodes (Xu et al., 1997b). An Eya2 transgene can rescue the eyeless phenotype in a fly eya mutant, implicating EYA2 as an important regulator of eye development (Bui et al., 2000). EYA2 also controls muscle development during organogenesis by regulating the expression of c-MYC, GDNF, and muscle determination genes such as MYOD, MRF4, and MYOG (Fougerousse et al., 2002; Grifone et al., 2007). EYA2 may also activate novel anti-hypertrophic signaling pathways to prevent cardiac hypertrophy and heart failure (Lee et al., 2009).

The EYA domain of EYA2 contains a HAD family Tyr phosphatase activity, which dephosphorylates the Y36 residue of ERβ (Yuan et al., 2014). Since phosphorylated Y36 is required for ERβ to recruit co-activators to its target promoters and subsequent activation of antitumor transcriptional pathways, EYA2-mediated dephosphorylation of Y36 counteracts ERβ dependent antitumor activity in breast cancer cell culture and mouse xenograft models (Yuan et al., 2014). In addition, the Tyr phosphatase activity of EYA3 was shown to dephosphorylate H2AX and leads cells to the DNA repair instead of apoptosis pathway upon DNA damage (Cook et al., 2009). Although EYA2 is also able to dephosphorylate H2AX (Krishnan et al., 2009), its direct role in DNA damage response has not been experimentally proven. Furthermore, the N-terminal region of EYA2 contains a Ser/Thr phosphatase activity, similar to EYA4 whose Ser/Thr phosphatase activity has been shown to play a role in innate immune response (Okabe et al., 2009).

Homology

The EYA Domain (ED) of human EYA2 has 64% sequence identity (83% similarity) with Drosophila EYA (Tadjuidje and Hegde, 2013), and 99% sequence identity (97% similarity) with mouse EYA2 (calculated by Clustal W). Within the human EYA family, EYA2 displays 83% sequence identity (92% similarity) with EYA1; 68% sequence identity (83% similarity) with EYA3; and 80% sequence identity (91% similarity) with EYA4 (Tadjuidje and Hegde, 2013).

Mutations

Germinal

No EYA2 mutants were reported.

Somatic

A number of genomic variants in normal individuals (Redon et al., 2006; Mills et al., 2006; de Smith et al., 2007; McCarroll et al., 2008; Park et al., 2010; Teague et al., 2010; Xu et al., 2011; Genomes Project et al., 2012; Wong et al., 2013) and cancer patients (COSMIC (Forbes et al., 2008) and TCGA (Cerami et al., 2012; Gao et al., 2013)) have been reported, although the correlation between these variants and any disease phenotypes is not yet clear. In addition, EYA2 is amplified in 14.8% of ovarian carcinomas and its protein product was detected in 93.6% of ovarian cancer specimens (Zhang et al., 2005). Aberrant overexpression of EYA2 is observed in breast cancer (Zhang et al., 2005; Farabaugh et al., 2012), lung adenocarcinoma (Zhang et al., 2005; Guo et al., 2009), prostate cancer (Zhang et al., 2005), desmoid tumors (Bacac et al., 2006), and urinary tract cancers (Zhang et al., 2005). The Oncomine database reveals that EYA2 is significantly overexpressed in multiple other tumor types, including infiltrating bladder urothelial carcinoma, superficial bladder cancer, glioblastoma, high grade squamous intraepithelial neoplasia, cervical cancer, and parathyroid gland adenoma (Patrick et al., 2013). On the other hand, decreased level of EYA2 by silencing methylations has been reported in colorectal cancers (Zou et al., 2007) and pancreatic cancer (Vincent et al., 2014).

Implicated in

Various cancers

Note

EYA2 is heavily implicated in breast tumorigenesis and metastasis. Knock down of EYA2 in SIX1-overexpressing MCF7 cells inhibits the ability of SIX1 to induce TGF-β signaling, epithelial-mesenchymal transition (EMT), and tumor initiating cell (TIC) characteristics, properties that are all associated with SIX1-induced tumorigenesis and metastasis (Farabaugh et al., 2012). Examination of the Wang and Van de Vijver public breast cancer microarray datasets demonstrated that over-expression of SIX1 and EYA2 together (but not either gene alone) is significantly associated with shortened time to relapse and metastasis and shortened survival (Farabaugh et al., 2012). Disruption of the SIX1-EYA2 interaction inhibits SIX1-EYA2 mediated breast tumor metastasis in mouse model (Patrick et al., 2013).

EYA2 has also been shown to dephosphorylate Y36 of ERβ and reduces ERβ-mediated growth inhibition of breast cancer cells (Yuan et al., 2014).

In addition, high SIX1/EYA2 expression correlates with decreased survival in large cell lung carcinoma and more advanced stage in ovarian serous adenocarcinoma (Patrick et al., 2013).

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