

Gene Section

Review

COPS2 (COP9 constitutive photomorphogenic homolog subunit 2 (Arabidopsis))

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Identity

Other names: ALIEN; CSN2; SGN2; TRIP15

HGNC (Hugo): COPS2

Location: 15q21.1

Note:

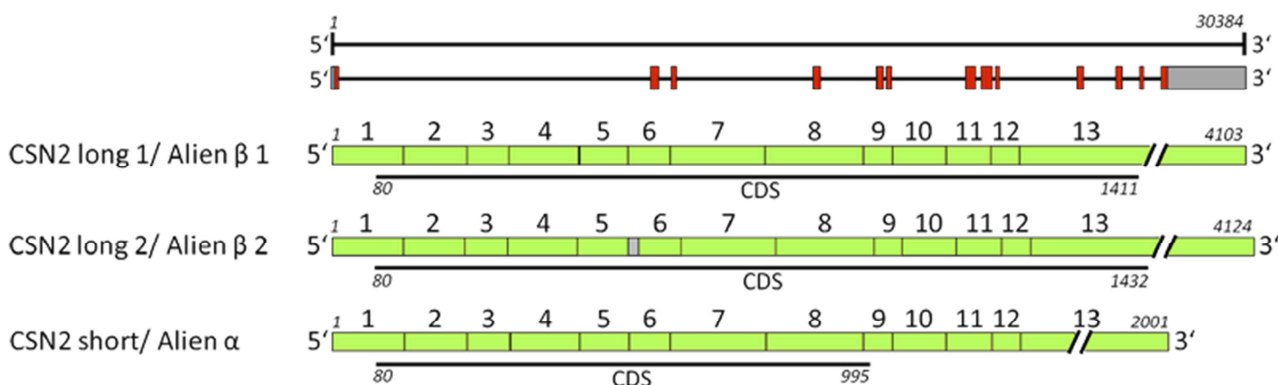
The beta casein is also abbreviated as CSN2.

DNA/RNA

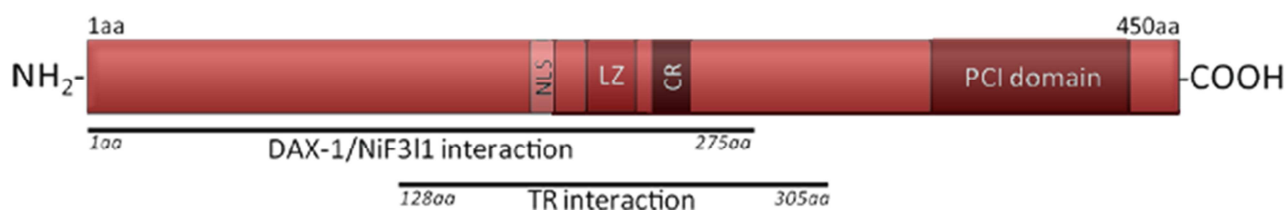
Transcription

The promoter region of CSN2 contains 4 NF-κB binding sites. Binding to these sites activates the transcription of CSN2 gene. Deletion of the C terminus of NF-κB abrogates the ability to induce CSN2 gene expression (Wu et al., 2009).

Furthermore, CSN2/Alien gene expression in vivo is activated by thyroid hormone receptor (TR) and thyroid hormone suggesting a regulatory feedback mechanism between TR and CSN2/Alien expression (Tenbaum et al., 2003).



The CSN2 gene is localized on chromosome 15q21.2 (top panel). A homologous sequence is located on chromosome 9q33.2 (not shown). The gene structure highlights intron/exon arrangement, whereas red boxes display coding sequence (CDS) and grey the untranslated regions. The lower panel exhibits the CSN2/Alien cDNA. The green boxes indicate the 13 exons and the black line below illustrates the coding sequences CDS. The grey box in isoform 2 highlights the additional inserted 21bp stretch which is specific for this splice variant. Differential functions of these isoforms are not yet known. The italic numbers illustrate the base pairs.



Schematic structure of the CSN2 protein (modified according to Akiyama et al., 2003). The N-terminal region contains a region for interaction with DAX-1/NiF31 (aa 1-275). The central part of the protein includes the nuclear localization signal (NLS), a leucine zipper (LZ) domain and a corepressor region (CR) which contains an I/LXXI/VI motif. The C-terminal region contains a PCI domain, might be used for interaction between CSN subunits (reviewed in: Wei and Deng, 2003). The numbers represent the amino acids (aa).

Protein

Description

Three isoforms are known:

CSN2 short/Alien a: 305 amino acids (aa); 36 kDa protein.

CSN2 long 1/Alien b1: 443 aa; 51.6 kDa protein.

CSN2 long 2/Alien b2: 450 aa; 52.4 kDa protein.

CSN2 activity can be regulated through phosphorylation and dephosphorylation (Kapelari et al., 2000).

Expression

Mouse *Csn2* is widely expressed in embryonic, fetal and adult tissues (Schaefer et al., 1998). Several mRNA levels have been described in mice: 1,8 kb ; 2,2 kb ; 4 kb and 6 kb (Schaefer et al., 1998; Altincicek et al., 2000; Tenbaum et al., 2003).

Localisation

CSN2 is localized in both the cytoplasm and the nucleus, predominantly being localized in the nucleus (Schaefer et al., 1998; Dressel et al., 1999; Tenbaum et al., 2003).

Function

CSN2 short/Alien a acts as a corepressor for nuclear hormone receptors (NHR). Originally in mammals, Alien was identified as an interacting protein of the thyroid hormone receptor (TR) in a ligand-sensitive manner (Lee et al., 1995). Moreover, Alien enhances TR-mediated gene silencing through its autonomous silencing function (Dressel et al., 1999). Additionally, the vitamin D receptor (VDR), the androgen receptor (AR) and the orphan receptor DAX-1 can also interact with Alien. Functionally Alien enhances gene silencing mediated by these nuclear receptors (Altincicek et al., 2000; Polly et al., 2000; Moehren et al., 2007). Notably, Alien seems to lack interaction with retinoid X receptor (RXR), retinoid acid receptor (RAR), estrogen receptor (ER), glucocorticoid receptor (GR) and germ cell nuclear factor (GCNF) (Dressel et al., 1999; Fuhrmann et al., 2000; reviewed in: Papaioannou et al., 2007).

Also, corepression function was identified by CSN2 short/Alien a for transcription factors involved in cell cycle regulation and DNA repair such as several members of the E2F transcription factor family (Escher

et al., 2007; reviewed in: Papaioannou et al., 2007). Alien is recruited to the E2F1 gene promoter repressing endogenous E2F1 gene expression *in vivo*. The data also suggest that Alien inhibits transactivation of E2F1, a positive regulator of cell cycle progression. In line with this, Alien represses cell cycle progression. Remarkably, the inhibition of E2F1-mediated transactivation is independent of retinoblastoma protein pRB (Tenbaum et al., 2007). pRB represses E2F1 transcriptional activation. It is not yet known whether Alien is able to substitute pRB function during cell cycle progression (Tenbaum et al., 2007). Furthermore, a direct interaction between Alien and pRB is detected. Interestingly, a pRB-mutant lacking silencing function also lacks interaction with CSN2 short/Alien (Escher et al., 2007).

In addition, Alien interacts with the highly conserved chromatin associated tumor suppressor proteins Inhibitor of growth 1 (ING1b) and 2 (ING2) *in vivo* and both p33ING1b and p33ING2 are known to induce premature cellular senescence. It is shown that p33ING proteins enhance Alien-mediated gene silencing (Fegers et al., 2007).

The recruitment of HDAC-activity is one mechanism by which Alien realizes its corepression functions (Dressel et al., 1999). However, it is suggested that Alien exhibits both HDAC-dependent and -independent options for gene repression (reviewed in: Papaioannou et al., 2007). Moreover, CSN2 short/Alien a interacts with nucleosome assembly protein 1 (NAP1) *in vivo* and *in vitro* regulating its activity through enhancing NAP1-mediated nucleosome assembly on DNA and thereby leading to gene repression (Eckey et al., 2007).

The CSN2 long/Alien b isoform is an essential part of the COP9 signalosome (CSN) complex which is highly conserved in eukaryotes and consists of eight subunits (reviewed in: Wie et al., 2008). The CSN complex plays a central role in the regulation of degradation of multiple proteins through the ability to de-neddylate cullin, which enables the association of cullin with CAND1, a negative regulator of the cullin-based E3 ubiquitin ligases (reviewed in: von Arnim, 2003; reviewed in: Wolf et al., 2003; Chamovitz, 2009; Wu et al., 2009). A role for CSN2 long/Alien b is suggested by the interaction between CSN2 and subunits of the 26S proteasome was already shown (Huang et al., 2005). The promoter region of the *Csn2* gene contains NF- κ B binding sites like other CSN subunits.

Accordingly, these members of the CSN complex are regulated by NF- κ B. Snail, a transcription factor, which is a part of the TGF- β pathway and is involved in inflammatory-triggered migration, invasiveness and metastasis of tumor cells, is stabilized by the induction of the CSN complex via NF- κ B (Wu et al., 2009). There are also COP9 subcomplexes with yet unknown functions (reviewed in: Wei et al, 2008).

Interaction of COP9 via CSN2 with p53 in tumors can raise the stability of p53, the most important protein involving in a variety of essential tumor suppressive functions and induction of cellular senescence. But in contrast to Snail, the lower turnover does not lead to an increase in transcription activity and therefore neither to an increased p21 expression nor to cell cycle arrest (Leal et al., 2008).

Moreover, CSN2 protein interacts physically with the anaphase-promoting complex (APC/C), a major regulator of the cell cycle and affects specifically its stability (Kob et al., 2008).

Homology

CSN2 is a highly conserved protein from humans to *Drosophila* (Dressel et al., 1999). CSN2 has homologies in any multicellular organism including plants. It is over 60% identical between animal and plant counterparts (Wei and Deng, 2003; Schwedheimer, 2004).

Originally, the name Alien was given to a gene in the *Drosophila* genome with an unknown function (Goubeaud et al., 1996). It shares high homologies with Thyroid hormone receptor-interacting protein 15 (TRIP15), a mammalian protein (Lee et al., 1995; Dressel et al., 1999).

Mutations

Note

So far natural occurring point mutations of CSN2 in association with cancer and other disease were not yet described.

Implicated in

Human tumors

Oncogenesis

Aberrant expression of CSN2/Alien seems to be associated with human tumors. CSN2 expression is lost in several human tumors. In thyroid tumors the loss of CSN2 is at least 50% (Leal et al., 2008). Moreover, high percentages of reduction (15-30%) of CSN2 mRNA level were observed in tumors of pancreas, breast, ovary, kidney, uterus and rectum (Leal et al., 2008).

It was shown by quantitative analysis that the CSN2 expression is reduced up to 50% in tumors of prostate, lung and colon (Leal et al., 2008).

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