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Gene Section
Review

CUX1 (cut-like homeobox 1)

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Identity

Other names: CASP, CDP, CDP/Cut, CDP1, COY1, CUTL1, CUX, Clox, Cux/CDP, FLJ31745, GOLIM6, Nbla10317, p100, p110, p200, p75

HGNC (Hugo): CUX1

Location: 7q22.1

DNA/RNA

Description

The human CUX1 gene is located on chromosome 7q22 (Scherer et al., 1993). It comprises 33 exons and spans 468 kb.

Five alternative splice variants have been identified. Most of the splicing sites are located in the regions downstream of exon 14 and 15 (Rong Zeng et al., 2000). Two alternative sites for transcript termination have been identified. Termination at UGA in exon 24 leads to production of CUX1 mRNA comprising exon 1-24. Elongation up to exon 33 results in alternative splicing and the production of CASP mRNA comprising exon 1-15 and 25-33 (Lievens et al., 1997; Rong Zeng et al., 2000).

The first transcriptional start site is located in exon 1 but transcription can be initiated at several sites in a 200 bp region upstream of exon 1 (Rong Zeng et al., 2000). Initiation within intron 20 leads to production of an mRNA coding for the shortened p75 isoform (Goulet et al., 2002).

Several putative translation initiation codons can be found in exon 1 but ATG at position 550 has been described as the predominant initiation site (Rong Zeng et al., 2000).

Protein

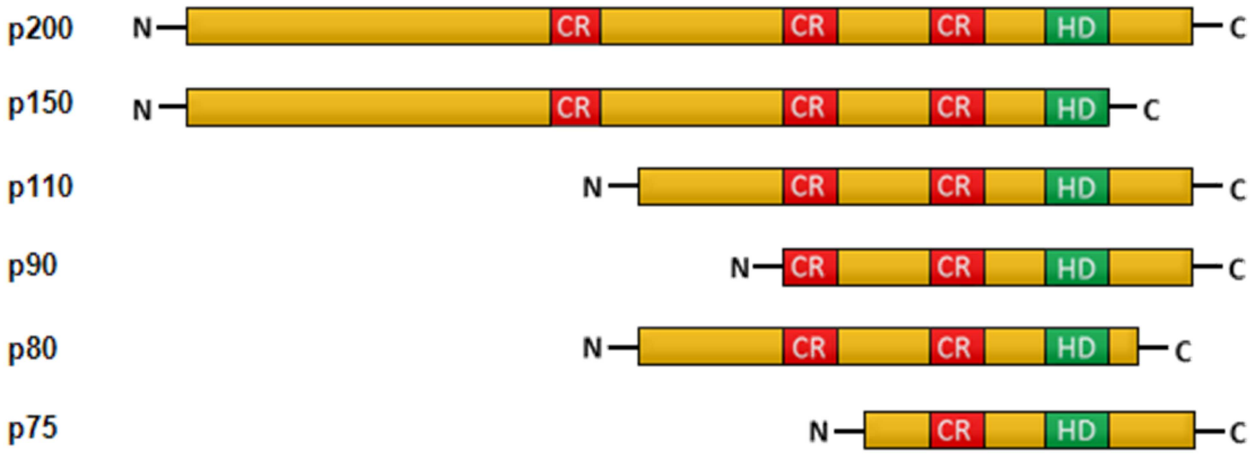
Description

The human full length CUX1 protein (p200) consists of 1505 amino acids and contains four DNA binding domains: three CUT-repeats and one CUT-homeodomain (Harada et al., 1994).

Several shortened CUX1 isoforms have been described that are named according to their molecular weight. CUX1 p75 is the product of a shortened mRNA that is generated by the use of an alternative transcription start site in exon 20 (Rong Zeng et al., 2000; Goulet et al., 2002). CUX1 p150, p110, p90 and p80 are generated by proteolytic processing of the full length protein by a nuclear isoform of Cathepsin L and other not yet identified proteases such as caspases (Goulet et al., 2004; Goulet et al., 2006; Maitra et al., 2006; Truscott et al., 2007).

The presence of DNA binding domains in the CUX1 isoforms determines their interaction with DNA and their transcriptional activity. The full length protein p200 shows unstable DNA binding, carries the CCAAT-displacement activity and functions predominantly as a transcriptional repressor. In contrast, the p110, p90, p80 and p75 isoforms show stable DNA binding and function both as transcriptional repressors or activators (Truscott et al., 2004; Goulet et al., 2002; Goulet et al., 2006; Moon et al., 2001). According to Maitra et al., the p150 isoform is incapable of DNA binding (Maitra et al., 2006).

Several posttranslational modifications are known to modulate the DNA binding activities of the CUX1 proteins.



Cux1 isoforms. The p75 isoform is the product of a shortened mRNA that is generated by the use of an alternative transcriptional start site. In contrast, the p150, p110, p90 and p80 isoforms are produced by proteolytic processing of the full length protein (p200). CR = cut repeat; HD = homeodomain.

Protein kinase C and Casein kinase II are able to phosphorylate serine or threonine residues within the cut repeats (Coqueret et al., 1998b; Li et al., 2007). Protein kinase A and cyclin A/Cdk1 phosphorylate specific serine residues in a region between the Cut repeat 3 and the homeodomain (Michl et al., 2006; Santaguida et al., 2001). PCAF acetyl-transferase is able to acetylate CUX1 on a lysine residue in the homeodomain (Li et al., 2000). Both, phosphorylation and acetylation have been shown to inhibit CUX1 DNA binding (Sansregret et al., 2010; Li et al., 2000). Consistent with this, dephosphorylation by Cdc 25A phosphatase is able to increase DNA binding of CUX1 (Coqueret et al, 1998a).

Expression

Early studies suggested that in mammalian cells, CUX1 represses genes that are upregulated in differentiated tissues. Furthermore, the expression of CUX1 might be restricted to proliferating and undifferentiated cells and is inversely related to the degree of differentiation (vanden Heuvel et al., 1996; Pattison et al., 1997; van Gurp et al., 1999). More recently however, studies in mice revealed that CUX1 is also expressed in terminally differentiated cells of many tissues (Khanna-Gupta et al., 2001; Ellis et al., 2001).

Increased CUX1 expression was found in various tumour types including multiple myelomas, acute lymphoblastic leukaemia, breast carcinoma and pancreatic cancer (De Vos et al., 2002; Tsutsumi et al., 2003; Michl et al., 2005; Ripka et al., 2007).

It has been shown that the cellular expression of CUX1 mRNA and protein is elevated following TGF-beta stimulation in many cell types including fibroblasts, pancreatic cancer cells, breast cancer cells and malignant plasma cells (Fragiadaki et al., 2011; Michl et al., 2005; De Vos et al., 2002). This regulation of CUX1 expression by TGF-beta is probably mediated by p38MAPK and Smad4 signalling (Michl et al., 2005).

Localisation

Studies indicate that phosphorylated CUX1 is preferentially localized in the cytoplasm whereas dephosphorylation leads to translocation into the nucleus (Sansregret et al., 2010).

Function

The vast majority of studies describes CUX1 as a transcriptional repressor (Lievens et al., 1995; Ai et al., 1999; Catt et al., 1999a; Catt et al., 1999b; Ueda et al., 2007). The repressor activity can be mediated by competition for DNA binding sites with transcriptional activators (Kim et al., 1997; Stünkel et al., 2000), by recruitment of histone deacetylases (Li et al., 1999) or by recruitment of histone lysine methyltransferases (Nishio and Walsh, 2004). CUX1 may also negatively regulate gene expression by binding to matrix attachment regions and by modulating their association with the nuclear scaffold (Banan et al., 1997; Stünkel et al., 2000; Goebel et al., 2002; Kaul-Ghanekar et al., 2004). In contrast, the mechanisms underlying its effects on transcriptional activation are less well understood.

CUX1 is involved in at least three cellular processes important for cancer progression: cell proliferation, cell motility/invasiveness and apoptosis.

Proliferation

Studies indicate that the pro-proliferative effects of CUX1 are mainly mediated by the p110 isoform. This isoform is produced by proteolytic cleavage of the full length protein occuring during G1/S-transition in the cell cycle (Goulet et al., 2004; Moon et al., 2001). Cells stably transfected with p110 CUX1 showed increased proliferation due to a shortened G1-phase whereas embryonic fibroblasts obtained from CUX1 knockout mice showed elongated G1-phase and less proliferation compared to cells isolated from wild-type mice (Sansregret et al., 2006).

A genome-wide location array for p110 CUX1 binding sites in transformed and non-transformed cell lines identified numerous CUX1 target genes that are related to proliferation and cell cycle progression (Harada et al., 2008). Most of these genes are activated by p110 CUX1 including DNA polymerase-alpha, cyclin A2 and cyclin E2. In contrast, other genes are repressed such as the CDK-inhibitor p21 (Truscott et al., 2003; Nishio and Walsh, 2004; Harada et al., 2008).

Cell motility

First evidence that CUX1 plays a role in cell motility originates from knockdown studies in fibroblasts and a panel of human cancer cell lines that revealed that depletion of CUX1 leads to decreased cell migration and invasion (Michl et al., 2005). In agreement with this, cells stably expressing p110 and p75 CUX1 show increased cell migration and invasion (Kedinger et al., 2009; Cadieux et al., 2009). Additionally, tail vein injection of cells stably expressing shRNA against CUX1 resulted in reduced formation of lung metastases, whereas injection of cells stably overexpressing CUX1 led to increased lung metastases (Michl et al., 2005; Cadieux et al., 2009).

The molecular basis for these effects on cell motility was in part elucidated in a genome-wide location analysis in several cell lines (Kedinger et al., 2009). In this study, CUX1 was found to inhibit the expression of genes that repress cell migration (e.g. E-cadherin, occludin) and to turn on the expression of genes that promote cell migration (e.g. FAK, N-cadherin, vimentin) (Kedinger et al., 2009). The regulation of these genes seems to be mediated both directly by binding of CUX1 to the gene promoters but also indirectly by modulation of transcription factors and signaling proteins involved in EMT (e.g. SNAI1, SNAI2, Src, Wnt5a) (Kedinger et al., 2009; Aleksic et al., 2007; Ripka et al., 2007). Additionally, several of the CUX1 target genes are known GTPases important for actin-cytoskeleton polymerization (Kedinger et al., 2009).

Apoptosis

Studies in pancreatic cancer cell lines showed that depletion of CUX1 by siRNA increases TNFalpha- and TRAIL-induced apoptosis whereas overexpression of CUX1 rescues from apoptosis. Additionally, treatment of xenograft tumours with siRNA for CUX1 lead to retarded tumour growth and increased apoptosis. These effects are at least in part explained by a positive regulation of the antiapoptotic protein BCL2 by CUX1 (Ripka et al., 2010a). Subsequently, the glutamate receptor GRIA3 was identified as another downstream target of CUX1 able to mediate its antiapoptotic effects (Ripka et al., 2010b).

Homology

Cut homeodomain proteins are highly conserved in evolution of metazoans. Homologues of the Drosophila melanogaster Cut protein have been described at least in human, dog and mouse (Neufeld et al., 1992; Andres et al., 1992; Valarché et al., 1993). In humans, a homologue gene, called CUX2, was described (Jacobsen et al., 2001).

Mutations

Note

A missense mutation affecting the homeodomain has been described in one patient suffering from acute myeloid leukaemia, the significance of which remains to be elucidated (Thoennissen et al., 2011).

Implicated in

Pancreatic cancer

Note

In pancreatic cancer CUX1 expression is elevated compared to normal pancreas tissue (Ripka et al., 2010a). Furthermore, an increased expression in high-grade tumours compared to low grade tumours was described (Michl et al., 2005).

The expression of CUX1 is accompanied by the overexpression of its downstream targets WNT5a and GRIA3 that, at least in part, mediate the proinvasive and proproliferative effects of CUX1 (Ripka et al., 2006; Ripka et al., 2010b).

Antiapoptotic effects of CUX1 in pancreatic cancer, that have been shown in in vitro studies and in xenograft models, are associated with a positive regulation of BCL2 and downregulation of tumour necrosis factor alpha and are, at least in part, mediated by the glutamate receptor GRIA3 (Ripka et al., 2010a; Ripka et al., 2010b).

Breast cancer

Note

In mammary carcinoma the CUX1 expression is increased in high-grade tumours compared to low grade tumours and a reverse correlation between CUX1 mRNA levels and the relapse free- and overall-survival was shown (Michl et al., 2005). Furthermore, is has been shown that the expression levels of the intron 20-initiated mRNA, that leads to the synthesis of the p75 CUX1 isoform, is specifically expressed in breast cancer and positively correlated with a diffuse infiltrative growth pattern (Goulet et al., 2002). Transgenic mice expressing p75 and p110 CUX1 under the control of the mouse mammary tumour virus-long terminal repeat developed breast cancer after a long latency period. This tumour development was accompanied by an increased activity of WNT-β-catenin signalling (Cadieux et al., 2009).

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