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CUX1

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Protein Symbols: CUX1, CUTL1 (cut-like homeobox 1)

Gene Symbol: CUX1

1. General function

The family of CUX/CDP-proteins is a group of transcription factors that are highly conserved among metazoans. They contain one homeodomain and at least one 'CUT-repeat'.

Early studies suggested that the expression of CUX1 in mammalians is restricted to proliferating and undifferentiated cells (20, 27, 28). However, more recent publications demonstrated that CUX1 expression can also be found in terminally differentiated cells of several tissues (5, 10). Proteolytic processing of the full length protein (p200) by Cathepsin L and other not yet identified proteases generates several isoforms of CUX1 (p150, p110, p90 and p80) that lack one or two of the three N-terminal CUT-repeats (7, 8, 15, 25). Another shortened isoform (p75) is generated by the usage of an alternative transcriptional start site (8, 23).

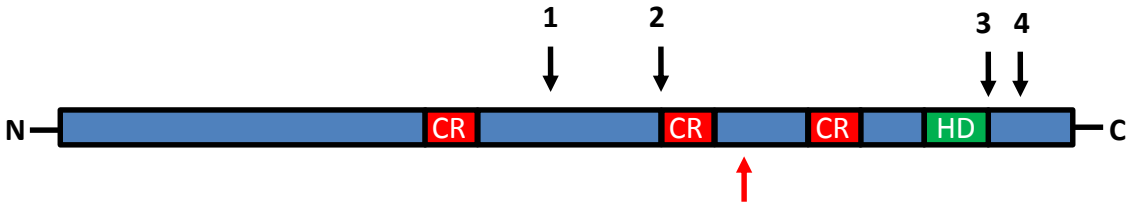

Fig.1: Domain structure of human full length-CUX1 (p200). Cut-Repeats are shown in red and the homeodomain in green. Black arrows indicate protease cleavage sites that lead to generation of the different CUX1 isoforms (p150 – 3; p110 – 1; p90 – 2; p80 – 1,4) . The usage of an alternative transcriptional start site generates the shortened isoform p75 (red arrow).

The presence of DNA binding cut-repeats in the CUX1 proteins influences their interaction with DNA and their transcriptional activity. In most circumstances, the function of CUX1 has been described as transcriptional repressor that represses gene expression by at least three different mechanisms: displacement of transcriptional activators, recruitment of histone deacetylases or recruitment of histone lysine methyltransferases (1, 3, 4, 11, 13, 14, 19, 26).

Numerous recent reports suggest that CUX1 functions also as transcriptional activator. However, only little is known about the underlying mechanisms.

Three main cellular processes have been described to be influenced by CUX1: cell proliferation, cell motility/invasiveness and apoptosis. The pro-proliferative effects are due to a shortened G1-phase mainly mediated by the p110 CUX1 isoform (6, 18, 24).

Several studies showed that *in vitro* knockdown of CUX1 decreases cell migration and invasion in different human cell lines whereas stable overexpression of p75 and p110 CUX1 increases cell motility and invasiveness (2, 9, 17). In tail vein injection experiments CUX1-shRNA expressing cells revealed reduced pulmonary colony formation, whereas CUX1 stably overexpressing cells led to an increased number of lung metastases (2, 17).

The anti-apoptotic effects of CUX1 have been shown in cancer cells *in vitro* and in xenograft mouse models (21, 22).

2. CUX1 in the Pancreas

CUX1 was found to be significantly overexpressed in human pancreatic cancer tissues compared to normal pancreas by in situ hybridization and immunohistochemistry (21). Furthermore the CUX1 expression level increases during cancer progression as high-grade tumors show higher CUX1 levels than low-grade tumors (17). One possible explanation for this observation is the increasing concentration of TGFbeta during pancreatic tumorigenesis as TGFbeta treatment stimulates expression of CUX1 mRNA and protein levels in several cell types including pancreatic cancer cells (17). Another known stimulator of CUX1 expression in pancreatic cancer cells is IGF1 that induces CUX1 expression via phosphatidylinositol 3-kinase (21).

Studies have shown that CUX1 has pro-invasive, pro-proliferative and anti-apoptotic effects in pancreatic cancer cells *in vitro* and in xenograft mouse models (16, 21, 22). SiRNA mediated knockdown of CUX1 increases TNFalpha- and TRAIL-induced cell death whereas overexpression of CUX1 rescues from apoptosis. Additionally, treatment of xenograft tumours with siRNA for CUX1 lead to retarded tumour growth and increased apoptosis (21, 22). Mediators of these effects are, at least in part, the CUX1 downstream targets WNT5A and the glutamate receptor GRIA3 (21, 22).

3. Tools for studies of CUX1

a. Antibodies

Rabbit polyclonal and mouse monoclonal antibodies have been raised against CUX1. Santa Cruz sells several goat, rabbit and mouse antibodies against CUX1. We used SC-13024 for WB and Immunoprecipitation but did not test it for other applications.

Several Anti-CUX1 antibodies are also available from Abcam. For IHC we use the mouse monoclonal antibody ab54583.

b. Mouse lines

Cadieux et al. created FVB mice transgenic for p75 and p110 CUX1 downstream of the mammary tumor virus (MMTV)-long terminal repeat that leads to expression specifically in mammary epithelial cells (2).

Ledford et al. generated a C57Bl/6 x C3H mouse expressing murine CUX1 under the control of the CMV promotor (12).

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