

Gene Section

Review

HOXC8 (homeobox C8)

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Abstract

Review on HOXC8, with data on DNA/RNA, on the protein encoded and functions in which this gene is implicated.

Identity

Other names: HOX3, HOX3A

HGNC (Hugo): HOXC8

Location: 12q13.13

Local order: Orientation: plus strand.

Note

This gene is one of several homeobox HOXC genes located in a cluster on chromosome 12.

The product of this gene may play a role in the

regulation of cartilage differentiation (Yueh et al., 1998).

It is also involved in chondrodysplasias and other cartilage disorders (Cormier et al., 2003; Kamel et al., 2009; Yueh et al., 1998).

DNA/RNA

Description

The HOXC8 gene is 3658 nucleotide long and consists of two exons.

There are 112 known SNPs in HOXC8 gene and most of them locate on the 5' end of the gene.

Transcription

The transcribed matured mRNA is 2290 nucleotide in length.

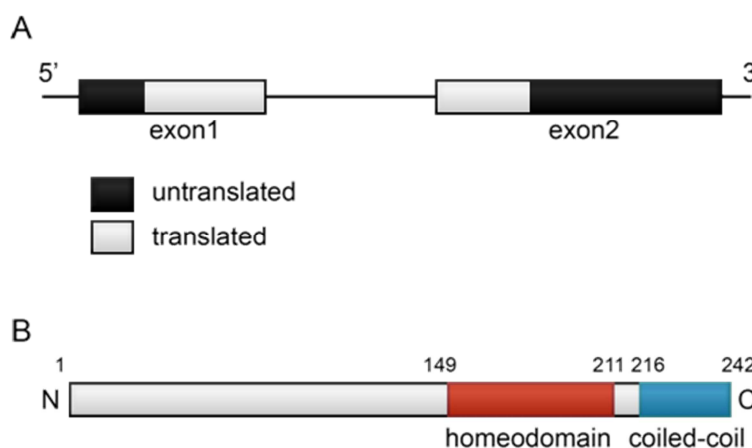


Figure 1. A. Schematic representation of human HOXC8 gene. B. Human HOXC8 protein with the indicated position of homeodomain (red color) and coiled-coil (blue color).

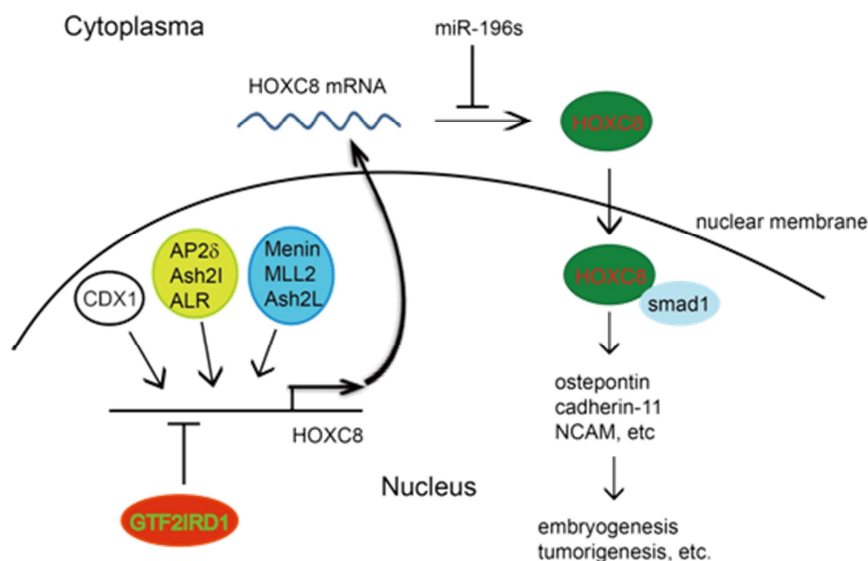


Figure 2. HOXC8 transcription can be regulated by CDX1, AP2d, menin and GTF2IRD1, respectively. The translation of HOXC8 protein can be blocked by the binding of miR-196s to its 3'UTR. As a transcription factor, HOXC8 is involved in the transcription of a variety of genes implicated in embryogenesis and tumorigenesis.

Transcription regulators: 1) CDX1, which is a member of the caudal-related homeobox transcription factor gene family, activates HOXC8 transcription by binding to its early enhancer (Schr et al., 2012). 2) Activating protein 2 delta (AP2 δ) transcription factor, which is one of AP2 five family members (AP2 α , AP2 β , AP2 γ , AP2 δ and AP2 ϵ), recruits Ash2I and ALR to the HOXC8 locus, resulting in H3K4me3-mediated gene activation (Tan et al., 2008). 3) Menin, which is a tumor suppressor gene associated with a syndrome known as multiple endocrine neoplasia type 1, binds to HOXC8 locus by associating with a histone methyltransferase complex containing two trithorax family proteins, MLL2 and Ash2L (MacConaill et al., 2006). 4) GTF2IRD1, which is a TFII-I family of transcription factors, interacts with HOXC8 early enhancer and represses the gene transcription (Thompson et al., 2007).

Protein

Description

HOXC8 protein contains 242 amino acids and is 27755 Da. HOXC8 contains a ~60 amino acid homeodomain with helix-turn-helix (HTH) motif which functions as a DNA binding domain. HOXC8 binds to DNA as monomers or homo- and/or heterodimers in a sequence-specific manner.

Expression

In mouse embryogenesis: HOXC8 is expressed in the neural tube and somatic mesoderm as well as in the prospective thorax. During embryogenesis, Hoxc8 is initially expressed with the identical boundaries in the mesoderm and neurectoderm.

Subsequently, Hoxc8 expression creeps forward and the boundaries in mesoderm and neural tube diverge. The gene is also expressed in both the neural tube and the somites in the prospective thorax (Pollock et al., 1992; Shashikant and Ruddle, 1996).

Cancers: Elevated HOXC8 expression is detected in breast cancer (Li et al., 2014; Li et al., 2010), cervical cancer (Alami et al., 1999), prostate cancer (Waltregny et al., 2002), esophageal cancer (Du et al., 2014), pancreatic cancer (Adwan et al., 2011).

Organs: HOXC8 is expressed in hematopoietic organs, brain, breast, placenta, liver, bone marrow, kidney, intestine and nervous systems, etc.

Cell types: HOXC8 is expressed on a variety of cell types, including fibroblasts, neurons, hair, adipose, skeletal and smooth muscle cells, lymph T cells, endothelial and epithelial cells, mesenchymal and stem cells, etc.

Translation regulation: Members of microRNA 196 family (miR-196a1, miR-196a2 and miR-196b) can bind to the 3'-UTR of HOXC8 mRNA, leading to the repression of HOXC8 translation (Li et al., 2010).

Localisation

Nucleus.

Function

HOXC8 serves as a transcription factor to regulate the expression of genes that are implicated in skeletal and neural development in embryogenesis and cancer progression.

Embryogenesis: Like other HOX proteins, HOXC8 plays an essential role in embryo anterior-posterior patterning and is responsible for skeletal

and neural development (Juan et al., 2006; Thickett and Morgan, 2002). Null mutants of HOXC8 show neuromuscular defects in the forelimb and skeletal defects in the ribs and vertebrae of the thorax (Le Mouelllic et al., 1992). Overexpression of a Hoxc8 transgene has been shown to cause cartilage defects by inhibiting the maturation and stimulating the proliferation of chondrocytes (Yueh et al., 1998).

Transcriptional regulation: As a transcription factor, microarray data indicate that HOXC8 regulates the expression of genes that are involved in cell proliferation, migration, adhesion, and differentiation (Lei et al., 2005). In response to bone morphogenetic protein (BMP) stimulation, HOXC8 activates the transcription of osteopontin (OPN) by interacting with Smad1 (Shi et al., 1999). In breast cancer cells, HOXC8 functions as a transcription factor to regulate cadherin 11 (Cdh11) transcription (Li et al., 2014; Li et al., 2011). ChIP assays demonstrate that HOXC8 can bind to the promoter of target genes including NCAM (neural cell adhesion molecule), PEDF (pigment epithelium-derived factor), ZAC1 (the zinc finger protein regulator of apoptosis) and PCNA (proliferating cell nuclear antigen) (Lei et al., 2006; Min et al., 2010). In addition, HOXC8 has also been identified as a transcription repressor. For instance, HOXC8 can downregulate the expression of Mgl1 and Smad6 by directly binding to the promoter regions of these 2 genes (Kang et al., 2010; Ruthala et al., 2011).

Stem cells: HOXC8 is expressed in vascular wall-resident multi-potent stem cells (VW-MPSCs), and silencing its expression significantly reduces cell sprouting capacity and increases expression of the smooth muscle cells marker genes (Klein et al., 2013).

Cancers: HOXC8 plays an essential role in cancer development, including breast, prostate, cervical and pancreatic cancers by facilitating cell migration and invasion (Adwan et al., 2011; Alami et al., 1999; Axlund et al., 2010; Du et al., 2014; Li et al., 2010).

Implicated in

Breast cancer

Note

Elevated expression of HOXC8 is found in invasive breast cell lines when compared with noninvasive breast cell lines. Immunohistochemistry staining shows that the level of HOXC8 is higher in breast cancer tissues than normal breast tissues (Li et al., 2010). Ectopic HOXC8 expression induces Cdh11 expression and promotes breast tumorigenesis (Li et al., 2012). Importantly, forced Cdh11 expression reverses the inhibitory effect in breast tumorigenesis elicited by HOXC8 knockdown (Li

et al., 2014). Moreover, the analysis of publically available human breast tumor microarray gene expression database demonstrates a strong positive linear association between HOXC8 and CDH11 expression ($R = 0.801$, $p < 0.001$). Survival analysis (Kaplan-Meier method, log-rank test) show that both high HOXC8 and CDH11 expression correlates with poor recurrence-free survival rate of patients (Li et al., 2014). Together, these findings suggest that HOXC8 promotes breast tumorigenesis by maintaining high level of CDH11 expression in breast cancer cells.

Prostate cancer

Note

HOXC8 is upregulated in primary prostate tumors, lymph node metastases and malignant prostate cell lines. HOXC8 overexpression has also been found to be correlated with loss of differentiation in prostate cancer cell lines and higher Gleason grade in prostate tissues.

These observations suggest that HOXC8 plays a role in the acquisition of invasion and metastasis of prostate cancer (Miller et al., 2003; Waltregny et al., 2002).

Pancreatic cancer

Note

In human pancreatic cancer cell lines, the level of HOXC8 mRNA is inversely related to their growth. Down-regulation of HOXC8 expression causes increased proliferation, migration and colony formation, which indicates that HOXC8 is a negative regulator of pancreatic cancer cell growth and metastasis.

In primary and metastatic tumor samples, immunohistochemistry staining shows that grading of primary carcinomas is negatively associated with the extent and intensity of HOXC8 staining (Adwan et al., 2011).

Cervical cancer

Note

The expression of HOXC8 is turned in in human cervical cancer cells while is off in normal cervical keratinocytes. This observation indicates that HOXC8 is probably involved in the process of cervical keratinocytes transformation (Alami et al., 1999).

Esophageal cancer

Note

Immunohistochemistry staining of 274 patients' tissues with esophageal squamous cell carcinoma (ESCC) show that HOXC8 expression has a strong correlation with 5-year survival rate and increases significantly from TNM (tumor & regional lymph node & metastasis) stage I to TNM stage III. This study indicates that HOXC8 expression may be

used as prognostic markers in patients with ESCC (Du et al., 2014).

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