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Gene Section
Review

CEBPA (CCAAT/enhancer binding protein (C/EBP), alpha)

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Abstract

Review on CEBPA, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: C/EBPa, CEBP

HGNC (Hugo): CEBPA

Location: 19q13.1

DNA/RNA

Description

Human C/EBPα is an intronless gene located on the minus strand of chromosome 19q.

Transcription

The C/EBPa mRNA (RNA messenger) consists of a short 5' unstranslated region (5'-UTR), a unique protein coding sequence (CDS) and a long 3'-UTR (Hendricks-Taylor et al., 1992).

Protein

Description

Human C/EBPα mRNA gives rise to two protein products by using two different translation starting sites (Figure 1 and 2) (Calkhoven et al., 2000). Compared to full-length C/EBPA protein, P42, the shorter P30 isoform lacks N-terminal 117 amino acids (Lin et al., 1993).

As a transcription factor, C/EBPA protein consists of DNA-binding domain (DBD) in its carboxyl-terminal (C-terminal), which is conserved between C/ebp family members (Leutz et al., 2011).

The highly conserved C-terminus includes the basic DNA binding leucine zipper domain (bZip).

The bZip domain in turn consists of a basic region that represents the DNA binding domain (DBD), the fork domain and the leucine zipper domain (LZ).

The bZip domain is indispensable for homodimerization and heterodimerization with other members of the C/EBP family.

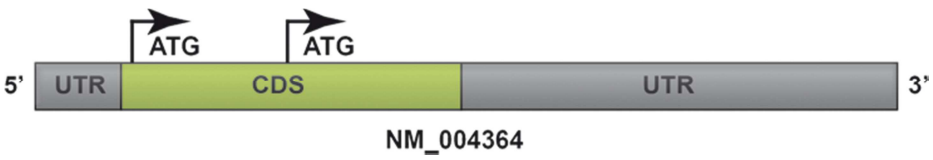

Figure 1: Human C/EBPa mRNA.

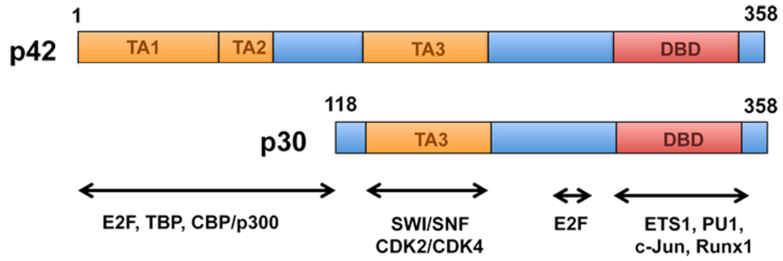

Figure 2: C/EBPa protein domains and interactions.

This region is also involved in the interaction with other transcription factors (e.g. E2F, PU.1, c-JUN, RUNX1 and ETS1) (McNagny et al., 1998; Yamaguchi et al., 1999; Ramji and Foka, 2002; Nerlov, 2004; Koschmieder et al., 2005; Leutz et al., 2011).
The N-terminus of C/EBPa consists of three transactivation domains (TA), which can interact with components of the transcriptional machinery (e.g. CBP/P300, TBP/TFIIB) (Nerlov and Ziff, 1995; Kovacs et al., 2003; Schwartz et al., 2003), cell cycle regulators (e.g. E2F, CDK2, CDK4) (Porse et al., 2001; Porse et al., 2006) and chromatin remodellers (e.g. SWI/SNF) (Pedersen et al., 2001).

Expression

C/EBPa is mainly expressed in terminally differentiated cells, such as mature adipocytes and myelomonocytic cells. C/EBPa is also found expressed in skin, intestine, lung, adrenal gland, mammary gland, ovary, prostate, placenta (Oh and Smart, 1998; Birkenmeier et al., 1989).

Localisation

C/EBPa protein is localized in nucleus.

Function

C/EBPa homozygous null mice lack white adipose tissues (Wang et al., 1995), as well as mature granulocytes and granulocyte-macrophage precursors (Zhang et al., 1997; Heath et al., 2004). In addition, forced expression of C/EBPa can direct uncommitted progenitors to differentiate into adipocytes and granulocytes (Freytag et al., 1994; Radomska et al., 1998; Nerlov et al., 1998). Further studies suggest that C/EBPa plays important roles in lineage determination by activating lineage-specific genes (Nerlov, 2004; Graf and Enver, 2009).
In hematopoiesis, C/EBPa is one of the key factors driving myeloid cell differentiation from hematopoietic stem cells by interacting with other proteins, such as the ETS family transcription factor PU.1, the ATP dependent chromatin remodeling complex SWI/SNF, the DNA modifying enzyme TET2 (McNagny et al., 1998; Koschmieder et al., 2005; Leutz et al., 2011; Kallin et al., 2012). Ectopic expression of C/EBPa leads to cell cycle arrest via direct interaction with the key cell cycle regulators CDK2/4 and E2F (Porse et al., 2001; Porse et al., 2006). The N-terminal truncated form of C/EBPa, P30, has been shown to act as a dominant negative regulator of the full-length form, P42. Modulation of P30 expression level in mice can alter normal adipogenesis and granulopoiesis (Kirstetter et al., 2008).
Notably, ectopic expression of C/EBPa in B and T-lymphocyte precursors results in transdifferentiation into functional macrophages (Xie et al., 2004; Laiosa et al., 2006; Bussmann et al., 2009; Di Tullio et al., 2011; Kallin et al., 2012). Interestingly, C/EBPa mediated conversion of B lymphoma cells into macrophages impairs significantly its tumorigenicity, providing a novel strategy for lymphoma treatment (Rapino et al., 2013). Moreover, a recent study showed that transient C/EBPa expression is also capable of facilitating the conversion of B cells into induced pluripotent stem cells (iPS cells) (Di Stefano et al., 2014).
Moreover, C/EBPa has been shown involved in lung development and airway epithelial differentiation (Cassel et al., 2000a; Cassel et al., 2000b; Cassel et al., 2002). The conditional deletion of C/EBPa gene in respiratory epithelium results in respiratory arrest and death soon after birth. This phenotype is associated with proliferation of immature type II alveolar cells, which causes epithelial expansion and loss of air space (Martis et al., 2006; Basseres et al., 2006).

Homology

C/EBPa belongs to the CCAAT/enhancer binging protein family and is highly conserved across vertebrate species. Sequence alignments show that C/EBP members share several conserved regions including the bZip and transactivation domains (Leutz et al., 2011).

Mutations

Note

Mutations of the C/EBPα gene have been detected in 7%-15% of Acute Myeloid Leukemia (AML) (Pabst et al., 2001b; Preudhomme et al., 2002;

Barjesteh van Waalwijk van Doorn-Khosrovani et al., 2003; Snaddon et al., 2003; Frohling et al., 2004; Lin et al., 2005), around 4% of Myelodysplastic Syndrome (MDS) and Chronic Myeloid Leukemia (CML) (Shih et al., 2005). In addition, two familial cases of AML harboring C/EBPA mutations have been reported (Smith et al., 2004; Renneville et al., 2009).

Germinal

Germ line mutations of C/EBPα have been described for two familial cases of AML. In one Inherited acute myeloid leukemia case, a heterozygous deletion of cytosine 212 has been reported (Smith et al., 2004). Recently, the second family contained a heterozygous insertion of cytosine at nucleotide 217 (Renneville et al., 2009). These mutations result in frameshifts, leading to a premature termination of full-length C/EBPa P42 isoform translation.
Nonetheless, the alternative C/EBPa P30 isoform translation could be potentially privileged. P30 isoform has dominant-negative activity on the full-length P42 isoform.

Somatic

It has been shown that 7%-15% of AML harbor somatic mutations of the C/EBPα gene (Pabst et al., 2001b; Preudhomme et al., 2002; Barjesteh van Waalwijk van Doorn-Khosrovani et al., 2003; Snaddon et al., 2003; Frohling et al., 2004; Lin et al., 2005). In addition, C/EBPα mutations have been detected in MDS and CML patient samples. These mutations can be basically divided into two categories: C-terminal in-frame ins/del mutations altering C/EBPA DNA-binding activities, and N-terminal out-of-frame ins/del mutations impairing translation of full-length P42 isoform and leading aberrant expression of P30 isoform, which has dominant-negative activity on P42 isoform. The majority of leukemias with biallelic C/EBPA mutations harbor one allele with C-terminal mutations and the other one with N-terminal mutations. Tumors with homozygous N'-terminal or C'-terminal mutations are relatively rare.

Implicated in

Acute myeloid leukemia (AML)

Disease

Mutations in C/EBPα have been identified in 7-15% of AML cases (Pabst et al., 2001b; Preudhomme et al., 2002; Barjesteh van Waalwijk van Doorn-Khosrovani et al., 2003; Snaddon et al., 2003; Frohling et al., 2004; Lin et al., 2005). A meta-analysis of a cohort of 1175 patients reported that C/EBPα mutations are preferentially identified in M1, M2 and M4 FAB subtypes and associated with normal karyotype (Leroy et al., 2005).

Prognosis

It has been shown that AML patients harboring C/EBPα mutations have favorable prognosis (Preudhomme et al., 2002).

Abnormal protein

C-terminal in-frame ins/del mutations can alter C/EBPa DNA-binding activities, and N-terminal out-of-frame ins/del mutations impairing translation of full-length P42 isoform and leading to aberrant expression of P30 isoform, which has dominant-negative activity on P42 isoform (Leroy et al., 2005).

Oncogenesis

Mouse models harboring biallelic (C-terminal and N-terminal) C/EBPα mutations suggested that the co-existence of these mutations can increase the proliferation of long-term hematopoietic stem cells (LT-HSC) and override normal HSC homeostasis, leading to expansion of premalignant HSC (Kirstetter et al., 2008; Bereshchenko et al., 2009). Moreover, the fusion oncoproteins AML1-ETO (t(8;21)), CBFb-HYH11 (inv(16)) and PML-RARa (t(15;17)) suppress C/EBPA mRNA expression and/or protein activity in AML (Pabst et al., 2001a; Truong et al., 2003; Cilloni et al., 2003).

B cell precursor acute lymphoblastic leukemia (BCP-ALL)

Note

t(14;19)(q32;q13)

Disease

It has been reported that C/EBPa is involved in several cases of BCP-ALL, although the prevalence of C/EBPa involved translocation need to be determined using larger cohorts (Chapiro et al., 2006; Akasaka et al., 2007; Jeffries et al., 2014). In these BCP-ALL cases, C/EBPa is aberrantly expressed by juxtaposition to the immunoglobulin gene enhancer upon its rearrangement with the immunoglobulin heavy-chain locus.

Oncogenesis

Aberrant expression of C/EBPa in BCP-ALL samples harboring t(14;19)(q32;q13) suggests that C/EBPa may have oncogenic function in this disease, which is in contrast to its onco-suppressor role in AML (Chapiro et al., 2006). Further biological studies need to be performed to clarify this hypothesis.

Non-small-cell lung cancer

Disease

The chromosomal region including C/EBPa was reported deleted in 50% stage II and IIIA lung adenocarcinomas (Girard et al., 2000). However, mutations of C/EBPa in lung cancer are rare. It has been as well reported that an upstream promoter region of the C/EBPa gene is hypermethylated in

approximately 65% of primary lung tumors (Tada et al., 2006). These evidences suggest that C/EBPa is a tumor suppressor in non-small-cell lung cancer.

Oncogenesis

Ectopic expression of C/EBPa in lung cancer cell lines results in significant growth arrest (Halmos et al., 2002; Costa et al., 2007). A transcriptional analysis identified that differentiation associated gene FoxA2 is a direct target gene of C/EBPa in lung cancer cell line (Halmos et al., 2004). Recently, using urethane-induced lung cancer model, it has been shown that C/EBPa expression is extinguished through p38alpha MAP kinase inactivation, leading to tumor progression (Sato et al., 2013), confirming a tumor suppressor role of C/EBPa in lung cancer.

Skin squamous cell carcinoma

Disease

Although C/EBPa expression has been found in human precancerous skin lesions (Actinic Keratoses) and normal epidermis, its expression is undetectable in invasive squamous cell carcinoma samples (Thompson et al., 2011), suggesting a possible role as a tumor-suppressor in skin cancer.

Oncogenesis

In normal epidermis, C/EBPa expression is located in basal and suprabasal keratinocytes (Maytin and Habener, 1998; Thompson et al., 2011). Forced C/EBPa expression in a skin cancer cell line inhibits cell proliferation (Shim et al., 2005). Moreover, C/EBPa-null mice are highly susceptible to 7,12-dimethylbenz[a]anthracene- and UVB-induced skin tumor development (Loomis et al., 2007; Thompson et al., 2011). Notably, It has been shown that down-regulation of C/EBPa in skin cancer cells is associated with oncogenic Ras activation (Shim et al., 2005; Loomis et al., 2007).

Prostate cancer

Disease

It has been shown that C/EBPa expression is down-regulated in prostate cancer sample comparing to normal prostate tissue (Yin et al., 2006). Interestingly, one study showed that C/EBPa expression is sequestered in cytosol, which could impair its transcription factor activity (Zhang et al., 2008). Although further studies need to be performed with larger prostate cancer cohorts for confirmation, these observations suggest an emerging tumor suppressor role of C/EBPa in prostate cancer.

Oncogenesis

C/EBPa is mainly expressed in basal layer in normal prostate. In most prostate adenocarcinoma samples, its expression level is low (Yin et al., 2006; Zhang et al., 2008). Forced expression of C/EBPa in prostate cancer cell lines can inhibit PSA (Prostate Specific Antigen) expression and regulate negatively androgen receptor (AR) signaling (Chattopadhyay et al., 2006; Yin et al., 2006; Zhang et al., 2010).

In addition, in AR-negative prostate cancer cell lines, ectopically expressed C/EBPA protein can physically interact with Ku proteins (Ku70, Ku80) and Poly [ADP-ribose] polymerase 1 (PARP-1), conferring prostate cancer cells an increased sensitivity to DNA-damaging agents (Yin and Glass, 2006).

Hepatocellular carcinoma

Disease

The expression of C/EBPa is reduced in hepatocellular carcinoma samples and higher expression of C/EBPa in hepatocellular carcinoma reversibly correlated with the tumor size and clinical stage (Tomizawa et al., 2003).

Oncogenesis

Forced C/EBPa expression in hepatoma cell lines impairs proliferation and tumorigenicity (Watkins et al., 1996). Liver specific C/EBPa knock-in mice are resistant, at least partially, to diethylnitrosamine-induced hepatocellular carcinoma formation. These observations suggest a tumor suppressor role of C/EBPa in hepatocellular carcinoma (Tan et al., 2005).

Head and neck squamous cell cancer

Disease

It has been reported that C/EBPa expression is down-regulated in squamous cell cancers in head and neck region. This down-regulation correlates with the degree of C/EBPa promoter methylation (Bennett et al., 2007).

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