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Gene Section
Short Communication

CEBPE (CCAAT/enhancer binding protein epsilon)

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Abstract

Review on CEBPE, with data on DNA, on the protein encoded, and where the gene is implicated.

Keywords
CEBPE; Transcription factor; Neutrophil specific granule deficiency; Acute lymphoblastic leukemia; Translocation.

Identity

Other names: CRP1

HGNC (Hugo): CEBPE

Location: 14q11.2

Location (base pair)
Starts at 23117306 and ends at 23119611 bp from pter (according to GRCh38.p7 Annotation Release 108, May 5 2016)

DNA/RNA

Description

CEBPE is located on chromosome 14q11.2 in a telomer-centromer orientation. Conflicting data have been published on the gene structure of CEBPE. According to the GRCh38.p7 assembly annotation (2016/03/21) the gene consists of two exons (1030 bp and 517 bp), which are partially coding and separated by a 759 bp intron (Figure 1a).
This is in conflict with some previously published papers. Yamanaka et al. (1997) described an alternative 3-exon-organization of the human CEBPE gene (Figure 1b). However, exon 1, as described by Yamanaka et al. contains a frameshift according to the GRCh38.p7 NCBI assembly.

Transcription

Various transcripts have been reported, resulting in four protein isoforms (Lekstrom-Himes 2001, Yamanaka 1997; Figure 1c). All transcripts share a common 3' end.

Protein

Description

CEBPE is a member of the CCAAT/enhancer-binding protein (C/EBP) family, which also includes CEBPA, CEBPB, CEBPG, CEBPD and CEBPZ (Ramji & Foka; 2002). A common structural feature of the C/EBP proteins is the presence of a highly conserved 55-65 amino acid sequence at the C-terminus which encodes a basic leucine zipper motif (bZIP domain) that functions as a dimerization domain. In the aminoterminal part all C/EBP proteins possess a DNA-binding domain with relative specificity for the CCAAT DNA motif. C/EBP proteins exert their physiological functions as either homo- or heterodimers. They can also interact with other bZIP- and non-bZIP transcription factors. Different protein domains have been characterized. The full-length CEBPE protein basically consists of an activation domain at the aminoterminal end, a repression domain in the center and the leucine zipper at the carboxyterminus (Williamson et al. 1998).

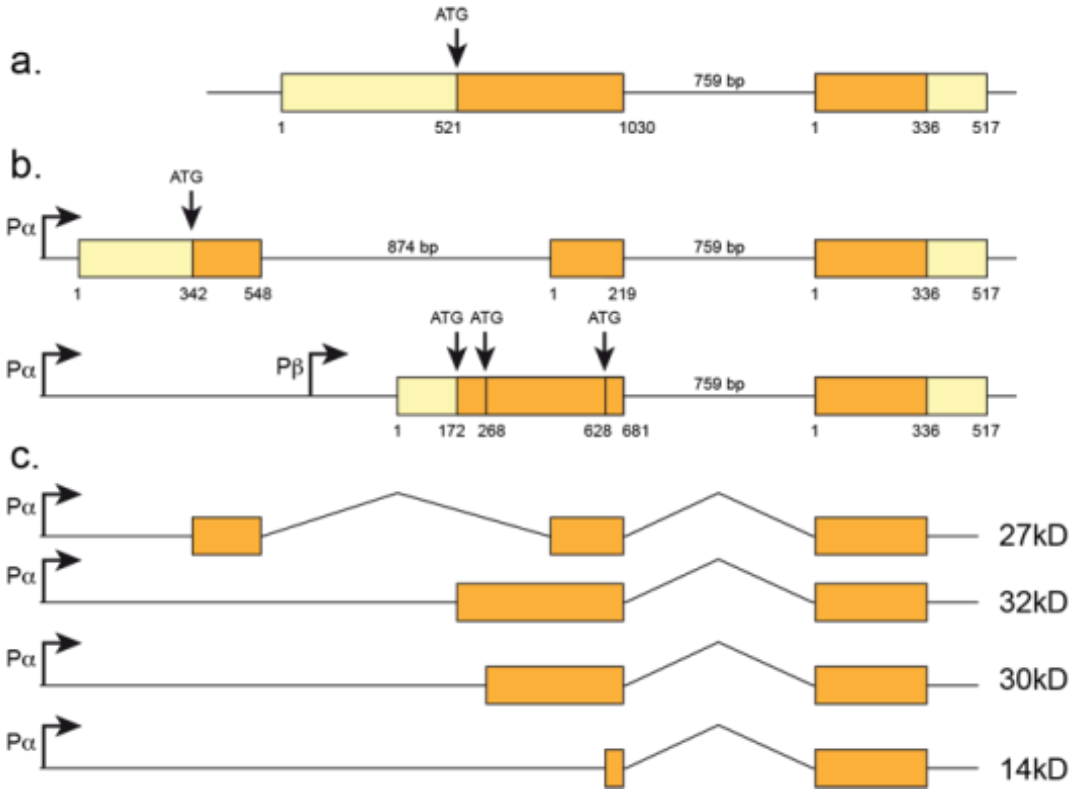

Figure 1: Human CEBPE gene and mRNA transcript: a. according to the GRCh38.p7 assembly annotation (2016/03/21); b. according to Yamanaka et al. (1997); c. transcripts based on the Yamanaka exon organization

At least four different CEBPE protein isoforms of 32, 30, 27, and 14 kDa have been described, but their functional significance is unclear (Lekstrom-Hines et al. 2001, Figure 1c).

The CEBPE translation product can undergo a number of post-translational modifications. Phosphorylation of CEBPE on threonine 75, located in the transactivation domain, is associated with increased DNA binding capacity and transcriptional activation (Williamson et al., 2005). Sumoylation of lysine residues within the repression domain has been found to modulate CEBPE function (Kim et al., 2005). Acetylation of lysine-121 and lysine-198 was found to be critical for terminal neutrophil differentiation (Bartels et. al., 2015).

Expression

CEBPE is predominantly expressed in cells of the hematopoietic system and to a much lesser extent in ovarian tissue (Yamanaka, et al., 1997). In normal hematopoietic cells CEBPE is preferentially expressed in myeloid-committed cells and the protein is virtually only detectable in metamyelocytes and myelocytes. The gene is also expressed in more immature myeloid cells but protein translation is repressed by miRNA-130a (Larsen et al., 2014).

The expression of CEBPE protein induces growth arrest, morphological differentiation, secondary granule proteins and has proapoptotic effects (Nakajima et al. 2006).

Localisation

Nuclear.

Function

CEBPE is a transcription factor, important for monocyte and granulocyte development. The transcription factor binds as a homodimer or heterodimer (with CEBPD) to specific DNA regulatory regions. Shorter CEBPE protein isoforms are hypothetical attenuators of the transcriptional activity of the long isoform.

Homozygous CEBPE knock-out (-/-) mice appear healthy at birth but survive only 2-5 months after birth, while heterozygous CEBPE knock-out mice appear normal. CEBPE (-/-) mice showed a marked increase in immature myeloid progenitors, increased numbers of morphologically abnormal neutrophils, that were functionally defect and lacked an oxidative burst, and decreased numbers of eosinophils. Thus it was concluded that CEBPE is essential for a normal terminal differentiation of committed granulocyte progenitor cells (Yamanaka, et al., 1997).

Implicated in

Neutrophil specific granule deficiency (SGD)

Some, but not all of the very few known patients with SGD harboured CEBPE mutations which led to loss of the dimerization domain; phenotypically, SGD patients show bilobed nuclei, impaired chemotaxis and bactericidal activity with susceptibility to severe bacterial infections (Gombart & Koeffler 2002).

Acute lymphoblastic leukemia (ALL)

The CEBPE single nucleotide polymorphism rs2239633 has been implicated as a susceptibility factor for the development of B lineage ALL in children and adults. The relative risk (odds ratio) conferred is 1.1-1.6 (Papaemmanuil et al., 2009; Burmeister et al. 2014).

t(14;14)(q11;q32) CEBPE/IGH and inv(14)(q11q32) CEBPE/IGH

CEBPE is found recurrently translocated to the immunoglobulin heavy chain locus (IGH) on 14q32 in acute lymphoblastic leukemia patients with inv(14)(q11q32)/t(14;14)(q11;q32). The translocation leads to an overexpression of CEBPE under the control of the immunoglobulin heavy chain gene promoters. At least five cases have been described (Akasaka et al. 2007).

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