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Gene Section
Review

CEBPA (CCAAT enhancer binding protein alpha)

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Identity

Hugo: CEBPA
Other names: C/EBPa
Location: 19q13.1

DNA/RNA

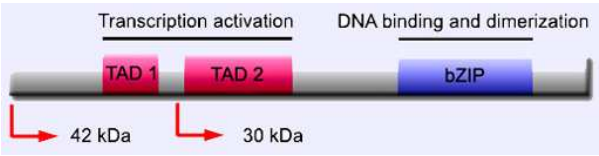
Description

CEBPA is a single exon gene located on the minus strand of chromosome 19q.

Transcription

The mRNA produced consists of a short 5'UTR containing a small 5'ORF, the coding region and a large 3'UTR.

Protein



C/EBPa protein domains
The basic region leucine zipper domain mediates DNA binding, homodimerization of C/EBPa and heterodimerization with other members of the C/EBP family. This region is also involved in mediating protein-protein interactions with other transcription factors involved in lineage determination and growth proliferation. N-terminal region transactivating domains mediate interactions with transcriptional machinery and proteins important in cell cycle control.
The CEBPA mRNA gives rise to two different translational isoforms by using different start codons within the same open reading frame by means of leaky ribosome scanning; the full length 42 kDa protein and a 30 kDa truncated form. These isoforms display contrasting functions in regards to gene activation and cell proliferation. Both isoforms can be detected within the cell and it is likely that the ratio of isoforms is important in mediating proliferation and differentiation control.

Expression

C/EBPa is expressed in many cell types and plays crucial roles in hepatocyte and adipocyte development, with highest concentrations in terminally differentiated cells. In hematopoiesis, C/EBPa is expressed in myeloid cells and drives granulocytic differentiation. C/EBPa is also found expressed in intestine, lung, adrenal gland, breast, ovary and placenta tissues.

Localisation

C/EBPa localises to the nucleus.

Function

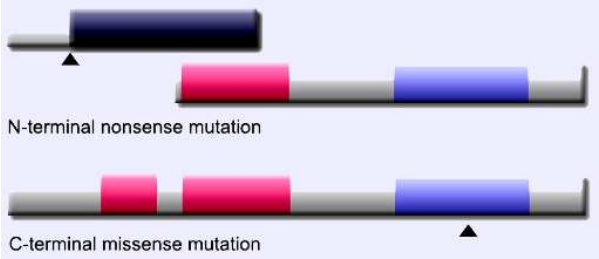
C/EBPa and its isoforms play important roles in lineage determination and gene activation in a variety of cell types by activating transcription from lineage-specific promoters. In hematopoiesis, C/EBPa is a key factor in driving the development of myeloid cells interacting with a variety of factors, including c-Myc, PU.1, and microRNAs. The truncated form of C/EBPa has been seen to act in a dominant negative regulatory manner in mice, abolishing normal C/EBPa function and causing a block in differentiation. In humans, the truncated protein selectively inhibits C/EBPa DNA binding but due to variable DNA affinity has a greater range of effects on differentiation.
Several pathways have been implicated as the means by which C/EBPa mediates cell cycle arrest and proliferation, including p21, cyclin-dependent kinases and the E2F complex via c-Myc. The 30 kDa isoform of C/EBPa lacks the domains required to mediate cell growth.

Homology

C/EBPa belongs to the family of C/EBP proteins and is conserved across a variety of vertebrate species.

Mutations

Note: Mutations in CEBPA occur in approximately 10% of all acute myeloid leukemias (AMLs).



N-terminal mutations abolish expression of full length 42 kDa protein, upregulating production of the 30 kDa isoform.
C-terminal mutations result in C/EBPa proteins with decreased DNA binding or dimerization activity.

Germinal

Germline mutations in CEBPA have been described in 2 familial cases of AML. The first family contained a heterozygous germline mutation of del (C) at nucleotide 212 which causes the premature termination of the protein at codon 158. The 30 kDa isoform is produced. Somatic mutation causing in frame duplication was also found in the C-terminal region of one patient on the other allele, which was not present in remission samples. The second family contained a heterozygous germline mutation of ins (C) at nucleotide 217 which causes the premature termination of the protein. The 30 kDa isoform is produced. Somatic mutations in the C-terminal region were found in two of the affected family members.

Somatic

Mutations in CEBPA tend to cluster to two regions.
The first group affect the N-terminal region of C/EBPa. These mutations are often insertions or deletions which cause frameshifts which cause premature truncation of the protein. In this case, translation is reinitiated at an internal ATG and the 30 kDa protein, which lacks the first transactivating domain, is produced.
Secondly, in-frame or missense mutations occur within the C-terminal region of C/EBPa, disrupting the basic zipper region and thus affecting DNA binding, protein interactions as well as homo and heterodimerization with other C/EBP family members.
Multiple mutations in CEBPA are common and often biallelic, although the allelic frequency of the mutations can change over the course of the disease. Mutations are generally maintained between presentation and replapse and therefore may be useful for monitoring minimal residual disease.

Implicated in

Acute myeloid leukemias

Disease

Mutations in CEBPA have been implicated in acute myeloid leukaemia, most often in association with FAB types M1 and M2, although it has also been found in M4 and M5 types. Mutations in CEBPA occur in approximately 10% of all AMLs and are associated with normal karyotype AML.

Prognosis

Mutations in CEBPA tend to confer favourable prognosis. Low levels of RNA expression of CEBPA have been noted in AML where it may reflect adverse prognosis.

Oncogenesis

CEBPA expression is downregulated in the presence of fusion protein AML1-ETO via inhibition of the CEBPA promoter.
Translation of the C/EBPa protein is suppressed by the fusion gene AML1-MDS1-EVI1 via the activation of calreticulin.
Pericentric inversion of chromosome 16, inv(16)(p13q22), which fuses the CBFB and MYH11 genes, with the latter encoding the smooth muscle myosin heavy chain (SMMHC) suppresses translation of the C/EBPa protein via calreticulin.
BCR-ABL fusion is able to suppress CEBPA protein translation via inhibitory action of the poly(rC)-binding protein hnRNP E2.
The involvement of CEBPA mutations in familial cases of AML, along with evidence of mutations persisting between presentation and relapse indicate that mutations in CEBPA are an early event in leukaemogenesis.

Although mutated CEBPA is primarily observed in AML, in rare cases it has been found to be mutated in myelodysplasic syndromes (MDS), lung tumours and prostate tumours. Down-regulation of CEBPA has also been observed in blast crisis chronic myeloid leukaemia, lung cancer, breast cancer and liver cancer.

t(14;19)(q32;q13) ⟶ IGH/CEBPA

Disease

CEBPA is rarely involved in translocations with other genes. However, in B-cell precursor acute lymphoblastic leukemia (BCP-ALL) the 3'UTR of CEBPA has been found to be translocated to the immunoglobulin heavy chain locus

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