CREBBP (CREB binding protein)

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Identity

Other names: CBP (cAMP Response Element-Binding Protein (CREB)-binding protein); RSTS (Rubinstein-Taybi syndrome); KAT3A

HGNC (Hugo): CREBBP

Location: 16p13.3

Local order: centromere-ADCY9-CREBBP-TRAP1-telomere.

DNA/RNA

Description

The gene spans about 155 kb; transcription from centromere to telomere, number of exons: 31.

Transcription

10 kb mRNA, with a 7.3 kb coding sequence, start codon in exon 1, stop codon in exon 31.

Protein

Description

2442 amino acids; 265351 Da; predict PI=8.83; Known domains are: KIX= CREB binding, Bromo= Bromodomain, Zn=zinc-finger (corresponding to cysteine-histidine rich regions), HAT= acetyl transferasic, Q= poly Glutaminic stretch. From the carboxy to the N-terminus: Q-Zn-HAT-Zn-Bromo-KIX-Zn. Reported isoform b (2402 aa) lacking aa406-444 (exon 5). Methylation of the KIX domain by CARM1 blocks association with CREB. Phosphorylated upon DNA damage, probably by ATM or ATR.

Expression

Wide expression; expression in the whole embryo as well brain; cDNA sources: mammary gland; lung; placenta; testis; lymph node; thymus; mouth; ear; kidney; embryonic tissue; larynx; pancreas; intestine; blood; heart; amniotic fluid; trachea; liver; thyroid; skin; connective tissue; uterus; eye; prostate; stomach; ovary; salivary gland; muscle; adrenal gland; bone marrow; adipose tissue; spleen; nerve; bone; bladder.
**Localisation**
Nucleus.

**Function**
Binds specifically to phosphorylate CREB and enhances its transcriptional activity toward cAMP-responsive genes; Acts as transcription co-activator by: i) enabling the interaction between different TF and RNAPoII complexes, ii) serving as molecular scaffold that brings enzymes to the promoter, iii) remodelling the chromatin favouring the open status, by histone and non-histone proteins acetylation. Essential role in embryogenesis, cell differentiation, apoptosis, and proliferation; Involved in the regulation of cell cycle during G1/S transition.

**Homology**
EP300

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**Implicated in**

### t(8;16)(p11;p13)/M4 ANLL -> MOZ/CBP

**Disease**
Acute non lymphocytic leukemia (ANLL) and treatment related ANLL (t-ANLL).

**Prognosis**
Poor: remission is obtained in half cases; survival is often less than 1yr.

**Cytogenetics**
+8 as an additional anomalies in half cases.

**Hybrid/Mutated gene**
5’ MOZ - 3’ CBP.

**Abnormal protein**
N-term finger motifs and acetyl transferase from MOZ fused to most of CBP, with a breakpoint in 5’ of the CREB binding domain of CBP.
**t(10;16)(q22;p13)/M4 ANLL → MYST4/CBP**

**Disease**
Acute myeloid leukaemia (AML) M4/M5a and therapy-related myelodysplastic syndromes (MDS). Only 4 cases described.

**Prognosis**
Poor, bad response to chemotherapy.

**Hybrid/Mutated gene**
5’ MYST4 - 3’ CBP.

**Abnormal protein**
In-frame fusion between MYST4 exon 17 and CREBBP exon 3. Variants fusing MYST4 exon 16 and CREBBP exon 5; MYST4 exon 17 and CREBBP exon 7 have been also described. CREBBP-MYST4 transcripts have been detected.

**t(11;16)(q23;p13)/t-ANLL → MLL/CBP**

**Disease**
Therapy related ANLL (t-ANLL); should be very close to the t(11;22)(q23;q13).

**Prognosis**
Likely to be poor.

**Hybrid/Mutated gene**
5’ MLL - 3’CBP.

**Abnormal protein**
N-term AT hook and DNA methyltransferase from MLL fused to most of CBP; variable brakpoint in CBP: either 5’ to the CREB binding domain (like in the t(8;16)), or just upstream the bromodomain.

**Rubinstein-Taybi syndrome**

**Note**
Due to CBP haploinsufficiency.

**Disease**
Rare autosomal dominant congenital disorder characterized by postnatal growth retardation and psychomotor developmental delay, skeletal anomalies (broad and duplicated distal phalanges of thumbs and halluces are a landmark sign) and specific facial dysmorphisms. The latter include down-slanted palpebral fissures, broad nasal bridge, beaked nose and micrognathia. In addition, patients with RSTS have an increased, although not well documented, risk of tumor formation.

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**Breakpoints**

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Localization of breakpoints affecting CREBBP and partner genes in leukaemia-associated balanced translocations.

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