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Gene Section

Review

BACH2 (BTB and CNC homology 1, basic leucine zipper transcription factor 2)

Malene Krag Kjeldsen, Karen Dybkaer, Jinghua Liu, Finn Skou Pedersen

Department of Haematology, Medical Center Aalborg Hospital Science and Innovation Center AHSIC, Sdr Skovvej 15, Aarhus University Hospital, DK-9000 Aalborg, Denmark (MKK, KD); Department of Molecular Biology, CF Mollers Alle 3, 1.130, Aarhus University, DK-8000 Arhus C, Denmark (JL, FSP)

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Identity

HGNC (Hugo): BACH2

Location: 6q15

Local order: Reverse strand.

DNA/RNA

Description

DNA: NCBI Reference Sequence: NC_000006.11;370316 bp DNA;BACH2 consists of 9 exons and 8 intervening introns.
RNA: NCBI Reference Sequence: NM_021813.2;9215 bp mRNA.

Transcription

Transcription produces at least four alternative spliced variants.

Pseudogene

By FISH, Sasaki et al. (2000) mapped the BACH2 gene to chromosome 6q15. Southern blot analysis determined that BACH2 is a single-copy gene (Sasaki et al., 2000).

Protein

Description

Reference sequence for BACH2 protein: NP_068585.1. BACH2 contains 841 amino acid residues with a molecular weight of 92536 Da.

BACH2 belongs to the bZIP family and CNC subfamily.

BACH2 contains a BTB domain for protein interaction in the N-terminal region starting at amino acid residue 37 to 103. In the C-terminus from amino acid residue 651 to amino acid residue 666 a basic DNA binding domain, followed by a hydrophobic leucine zipper domain ranging from amino acid residue 674 to 695 responsible for dimerisation.

The four alternative spliced variants generate four different proteins:

1) BACH2-003, transcript ID: ENST00000257749 and protein ID: ENSP00000257749. This transcript contains all 9 exons and has the full length transcript at 9215 bps and a full length protein with 841 aa.

2) BACH2-005, transcript ID: ENST00000343122 and protein ID: ENSP00000345642. This transcript contains 7 exons (1, 4, 5, 6, 7, 8, 9) resulting in a transcript with 3981 bps and a protein with 841 aa.

3) BACH2-002, transcript ID: ENST00000406998 and protein ID: ENSP00000384145. This transcript contains only 4 alternative exons (1, 4, 5, 6) producing a transcript at 780 bps and a protein with 81 aa. This alternative protein only contains the BTB domain.

4) BACH2-007, transcript ID: ENST00000453877 and protein ID: ENSP00000397668. This transcript contains only 5 alternative exons (1, 2, 4, 5, 6), producing a transcript at 868 bps and 81 aa. This alterniative protein only contains the BTB domain.

Liu et al. have, in mice, identified an alternative promoter and new isoforms of BACH2 by using murine insertional mutagenesis (Liu et al., 2009).

Related proteins:

BACH1 and BACH2 are highly homologous proteins with significant similarity to each other in the bZIP and BTB domains. But the expression pattern and function of the two proteins are different. BACH1 is more

ubiquitously expressed whereas BACH2 expression is restricted to mononuclear and neuronal cells. (Shim et al., 2006; Hoshino and Igarashi, 2002; Muto et al., 1998; Oyake et al., 1996).

Expression

BACH2 is expressed mainly in B-lymphoid cells and in the fetal brain (Muto et al., 1998; Hoshino and Igarashi, 2002). During B cell differentiation BACH2 is expressed from the pro-B cell to the mature B-cell stages but is absent in the plasma cell stage (Igarashi et al., 2007). Its expression is also silenced in primary plasma cells (our unpublished observation). BACH2 is expressed in umbilical cord blood CD4+ T cells (Lesniewski et al., 2008).

Localisation

BACH2 is predominantly cytoplasmic and migrates to the nucleus upon oxidative stress where it functions as a proapoptotic factor (Muto et al., 2002; Hoshino et al., 2000).

Function

BACH2 protein is a transcriptional repressor or activator. BACH2 forms heterodimers with small Maf oncoproteins (MafF, MafG, MafK) through the BTB domain. It binds to Maf recognition elements (MARE) through the DNA binding domain bZIP. It plays important roles in coordinating transcription activation and repression by MAFK (by similarity) (Oyake et al., 1996).

BACH2 in B-cell differentation:

BACH2 is critical for antibody responses including class switch recombination (CSR) and somatic hypermutation (SH) of immunoglobulin genes (Muto et al., 2004). BACH2 and Bcl-6 cooporates to repress Prdm1, and thereby regulating B-cell differentiation through the germinal center (Ochiai et al., 2008).

Neuronal differentiation:

BACH2 seems to be involed in neuronal differentiation, by upregulating both cytoplasmic and nuclear p21 protein levels. P21 is a cdk inhibitor known to arrest the cell cycle. In N1E-115 cells regulation of differentiation involves a down regulation of cellular proliferation (Shim et al., 2006).

Immune response:

BACH2 is involved in the antiviral response triggered by dsRNA or dsDNA molecular patterns (Hong et al., 2008).

Homology

HomoloGene (NCBI) BACH2 conserved in Euteleostomi. Genes identified as putative homologs:

NP_068585.1 BACH2 Homo sapiens

XP_539044.2 BACH2 Canis lupus familiaris

XP_618496.2 BACH2 Bos Taurus

XP_232858.3 RGD1562865 Rattus norvegicus

XP_419833.2 BACH2 Gallus gallus

XP_682933.2 bach2 Danio rerio

Mutations

Note

There are 11 SNPs in coding regions of human BACH2 of which 4 are encoding missense protein residues (NCBI dbSNP).

Bach2 is considered a B-cell specific tumor suppressor since loss of heterozygosity (LOH) is frequently observed for non-hodgkin lymphomas (Sasaki et al., 2000).

High throughput screens using retroviral and transposon insertion into mouse models have identified BACH2 as a common insertion site (CIS) (http://rtcgd.abcc.ncifcrf.gov/). BACH2 expression is in these models disrupted or activated in the resulting B cell tumours.

Homozygous null mice display impaired B cell differentiation and reduced B cell numbers.

Implicated in

Diffuse large B-cell lymphoma (DLBCL)

Note

BACH2 expression was immunohistochemically examined for 108 DLBCL patients and for 2/3 of cases staining intensity in the cytoplasm of the tumor cells was weaker than that in the endothelial cells in the same specimens (Sakane-Ishikawa et al., 2005).

The translocation between the Bcl-2 and the immunoglobulin heavy-chain (IgH) gene, t(14;18)(q21;q34), is a common genetic alteration in follicular and DLBCL lymphomas, bringing the antiapoptotic Bcl-2 gene under regulation of the active IgH promoter in B-cells. This translocation should result in an upregulation of Bcl-2 due to the activity of the IgH promoter in B-cells. Green et al. demonstrated that patients with t(14;18) and a high expression of BACH2 had significantly lower Bcl-2 expression from the t(14;18) translocation (Green et al., 2009).

Disease

DLBCL, a lymphoma entity characterised by an agressive malignancy of mature B-lymphocytes, is the most common type of B-NHL accounting for 30-40%. Bach2 is a B-cell specific tumor
suppressor and relatively high frequencies of loss of heterozygosity (LOH), 20% in 25 cases, was detected for Bach2 (Sasaki et al., 2000).

Prognosis

Most patients respond initially to chemotherapy, fewer than half of the patients achieve a durable remission. At present, the International Prognostic Index (IPI) is the most widely used for prediction of outcome in patients with aggresive NHL. It incorporates patient age performance status, serum lactate dehydrogenase (LDH), clinical stage, and the number of extranodal lesions. Bach2 expression level has proven to be a useful marker to predict disease-free and overall survival of patients with DLBCL, where a favorable

prognosis is correlated with a high expression level of Bach2 protein (Sakane-Ishikawa et al., 2005), perhaps because over-expression of Bach2 increased cellular toxicity of anticancer drugs that generate reactive oxygen species (Kamio et al., 2003).

Chronic myeloid leukemia (CML)

Note

Comparison of the mRNA profile of a CML cell line, BV173, before and after imatinib treatment revealed an accumulation of BACH2 mRNA upon BCR-ABL kinase inhibition (Vieira et al., 2001). This up-regulation of BACH2 by imatinib was seen in lymphoid BCR-ABL1-positive cell lines, as well as in CD34+ cells from CML patients, but not in myeloid BCR-ABL1-positive cell lines. However, the relationship between the regulation of BACH2 and higher order nuclear structure in CML and human B cells remains unclear (Vieira et al., 2001; Yoshida et al., 2006).

Disease

CML is a myeloproliferative disorder of the hematopoietic stem cell caused by a t(9;22)(q34;q11) translocation that generates the Philadelphia (Ph) chromosome. This translocation result in the expression of the fusion oncoprotein, Bcr-Abl, with uncontrolled tyrosine kinase activity. Bcr-Abl phsphorylates several substrates that activate multiple signaling pathways, including Ras, signal transducer and activator of transcription-5 (STAT-5), Janus kinase 2 (Jak-2) and others. This abnormal signaling leads to increased proliferation, reduced adhesion to the bone marrow stroma and extracellular matrix, and inhibition of the apoptotic response to mutagenic stimuli, giving rise to the malignant phenotype of CML (Yoshida et al., 2006).

Burkitt's lymphoma

Note

Epstein-Barr virus is an oncogenic virus, present in Burkitt's lymphoma cells. The Raji cell line (Burkitt's lymphoma) has no BACH2 expression and enforced BACH2 expression generates a marked reduction of clonogenic activity (Sasaki et al., 2000). Takakuwa and co-workers demonstrated that the EBV chromosome was present in intron 1 of the BACH2 gene located on chromosome 6q15. As BACH2 is a putative tumour suppressor gene, they suggest that loss of BACH2 might contribute to lymphomagenesis (Takakuwa et al., 2004).

Ovarian cancer

Note

Dysregulated androgen response in ovarian cancer results in transcriptional upregulation of BACH2 and acetylchrolinesterase. Both cytoplasmic BACH2 and acetylcholinesterase immunostaining were significantly increased in ovarian cancer relative to benign cases. Accumulation of nuclear BACH2 correlated with decreased time to disease recurrence (Motamed-Khorasani et al., 2007).

Diabetes type 1

Note

Type 1 diabetes is a common multifactorial with a strong genetic component. Genome wide association studies reveal that BACH2 is associated with Type 1 diabetes (Grant et al., 2009; Cooper et al., 2008).

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