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Gene Section

Review

MAFB (v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog B)

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Abstract

The MAFB protein is a basic leucine zipper (bZIP) transcription factor that plays important roles both in development and in the regulation of lineage-specific hematopoiesis. This gene contains no introns. The abnormal function of MAFB has been implicated in multiple myeloma, myeloid leukemias, multicentric carpotarsal osteolysis, Dupuytren's disease and nonsyndromic cleft lip.

Keywords

MAFB, KRML, MCTO, multiple myeloma, myeloid leukemia, multicentric carpotarsal osteolysis

Identity

Other names: KRML, MCTO

HGNC (Hugo): MAFB

Location: 20q12

DNA/RNA

Note

The MAFB open reading frame is encoded by a unique exon.

Description

MAFB gene maps to chromosome 20q11.2-q13.1, consists of a single exon and spans around 3 kb (Cordes and Barsh, 1994; Sieweke et al., 1996).

Transcription

1 exon, 3378 bp.

Ubiquitous expression of MAFB.

Protein

Note

MAF family members, such as MAFB, are basic region/leucine zipper transcription factors that affect transcription positively or negatively, depending on their partner proteins and the context of the target promoter (Wang et al., 1999).

Description

Sequence length: 323 aa.

Molecular mass of 35792 Da.

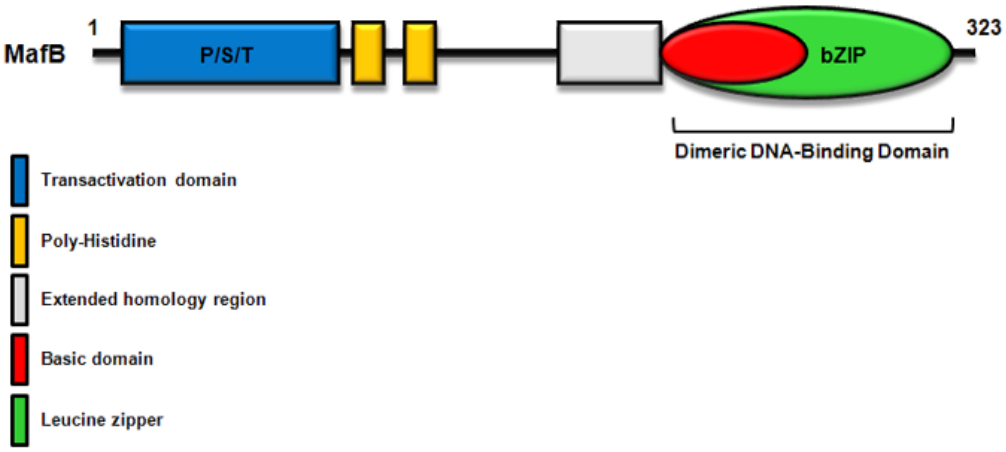
Sequence similarities: MAFB belongs to the bZIP family. MAF family contains one bZIP (basic-leucine zipper) domain.

Expression

MAFB is expressed in the digestive, endocrine and in immature myeloid/monocytic cells but not in lymphocytes.

Localisation

Intracellular, nucleus.



Protein structure of MAFB.

Function

Transcription factor; DNA binding protein.

MAFB acts as a transcriptional activator or repressor. It plays a role in erythroid differentiation and in the haematopoietic system it is expressed in immature myeloid/monocytic cells but not in lymphocytes (Kelly et al., 2000). MAFB plays a pivotal role in regulating lineage-specific hematopoiesis by repressing ETS1-mediated transcription of erythroid-specific genes in myeloid cells (Zanocco-Marani et al., 2009). It is also required for monocytic, macrophage, podocyte and islet beta cell differentiation (Kelly et al., 2000; Sevinsky et al., 2004; Bakri et al., 2005; Gemelli et al., 2008; Vanhoose et al., 2008; Aziz et al., 2009). SUMO modification controls its transcriptional activity and ability to specify macrophage fate (Tillmanns et al., 2007). Together with MAFA, MAFB regulates PDX1 transcription in pancreatic beta cells (Vanhoose et al., 2008). It is also involved in renal tubule survival and F4/80 maturation (Moriguchi et al., 2006). This protein activates the insulin and glucagon promoters. Together with PAX6, MAFB transactivates weakly the glucagon gene promoter through the G1 element (Gosmain et al., 2010). MAFB induces osteoclastogenesis and is essential for normal renal development (Zankl et al., 2012). It is a regulator of hindbrain segmentation and interacts with the ICD of LRP1 through a leucine zipper domain (Petersen et al., 2004). It is involved either as an oncogene or as a tumor suppressor, depending on the cell context, in multiple myeloma and myeloid leukemia development (Eychène et al., 2008).

It is implicated in the following physiological biological processes: rhombomere 6 development; segment specification; negative regulation of erythrocyte differentiation; inner ear morphogenesis; sensory organ development; transcription, DNA-dependent; thymus development; T cell differentiation in the thymus; positive regulation of transcription from RNA polymerase II promoter; respiratory gaseous exchange; rhombomere 5 development; brain segmentation.

Homology

MAFB shares 84% amino acid identity with its murine homolog.

Implicated in

Multiple myeloma

Disease

Multiple myeloma, also known as plasma cell myeloma, is a cancer of plasma cells. In multiple myeloma, collections of abnormal plasma cells accumulate in the bone marrow, where they interfere with the production of normal blood cells. Most cases of multiple myeloma also feature the production of a paraprotein - an abnormal antibody which can cause kidney problems. Bone lesions and hypercalcemia (high blood calcium levels) are also often encountered. MAFB is a specific marker for the prognostic unfavorable t(14;20)(q32;q12) in multiple myeloma patients (Stralen et al., 2009).

Prognosis

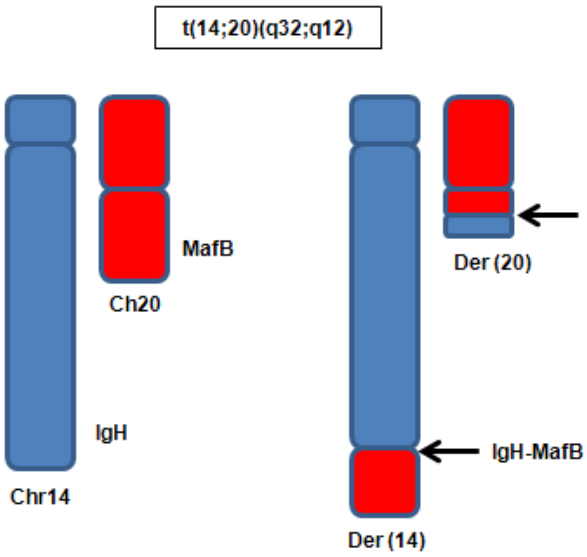
With high-dose therapy followed by autologous stem cell transplantation, the median survival has been estimated to be approximately 4.5 years in 2013, compared to a median of approximately 3.5 years with "standard" therapy (Child et al., 2003). Overall the 5-year survival rate is around 35% (Seiter et al., 2013).

Cytogenetics

Translocation t(14;20)(q32;q12).

Hybrid/Mutated gene

IGH-MAFB given rise to and aberrant expression of MAFB.



Translocation t(14;20) is implicated in multiple myeloma. Chromosomal translocations of the immunoglobulin heavy chain (IgH) gene region at 14q32 are regularly involved in B lymphoid malignancies. The recurrent translocation t(14;20)(q32;q12) in multiple myeloma results in aberrant expression of MAFB.

Abnormal protein

No fusion protein. Only aberrant expression of MAFB.

Oncogenesis

Human plasma cell neoplasias are thought to develop from either differentiated B cells or plasma cells. However, when the expression of MAF oncogenes (associated to human plasma cell neoplasias) are targeted to mouse B cells, the resulting animals fail to reproduce the human disease. An engineered transgenic mice that express MafB in haematopoietic stem/progenitor cells (HS/PCs) reproduced human multiple myeloma disease suggesting that, mechanistically, the haematopoietic progenitor population can be the target for transformation in MafB-associated plasma cell neoplasias (Vicente-Dueñas et al., 2012b). And the loss of p53 exacerbates this tumor stem cell reprogramming process (Vicente-Dueñas et al., 2012a).

Myeloid leukemia

Note

MAFB gene is deleted in myeloid leukemias (Wang et al., 1999). A deletion of the long arm of chromosome 20 [del(20q)] is a recurring abnormality in a wide spectrum of myeloid disorders. Loss of genetic material from 20q seems to confer a proliferative advantage to myeloid cells, possibly through loss of function of a tumor suppressor gene (Wang et al., 1998).

Disease

Myeloid leukemia is a type of leukemia affecting myeloid tissue. There are two main types, acute myeloid leukemia and chronic myelogenous leukemia.

Cytogenetics

Deletion of the long arm of chromosome 20.

Multicentric carpotarsal osteolysis (MCTO)

Note

Multicentric carpotarsal osteolysis is due to a heterozygosity missense mutations in the MAFB gene. The mutations were clustered within a 51-bp region of the single exon of MAFB at the N-terminal transcription activation domain. The allelic variants are: THR62PRO; SER70ALA; SER70LEU; PRO71SER; PRO71LEU and PRO54LEU (Zankl et al., 2012).

Disease

Defects in MAFB are the cause of multicentric carpotarsal osteolysis syndrome (MCTO). MCTO is a rare skeletal disorder, usually presenting in early childhood with a clinical picture mimicking juvenile rheumatoid arthritis. Progressive destruction of the carpal and tarsal bone usually occurs and other bones may also be involved.

Chronic renal failure is a frequent component of the syndrome.

Mental retardation and minor facial anomalies have been noted in some patients. The main clinical features are progressive destruction of the carpal and tarsal bone and other bones may also be involved, associated with chronic renal failure, mental retardation and minor facial anomalies.

Dupuytren's disease (DD)

Note

Microarray analysis identified significantly upregulatation of MAFB among other genes in Dupuytren's disease. MAFB immunohistochemistry

showed positive staining in 50% of the DD specimens studied (Lee et al., 2006).

Disease

Dupuytren's disease is characterized by fibroblastic proliferation of the palmar fascia, often leading to flexion contracture in the hand, where the fingers bend towards the palm and cannot be fully extended (Lee et al., 2006).

Dupuytren's contracture progresses slowly and is often accompanied by some aching and itching. In patients with this condition, the palmar fascia thickens and shortens so that the tendons connected to the fingers cannot move freely. Incidence increases after the age of 40.

Nonsyndromic cleft lip (NSCLP)

Note

Nonsyndromic cleft lip with or without cleft palate is a common isolated orofacial birth defect. The etiology of NSCLP is complex with both genetic and environmental factors implicated, but to date approximately only 20% of the genetic susceptibility has been identified (Vieira, 2008). Genome-wide association studies support for the association of MAFB and NSCLP (Yuan et al., 2011).

Disease

Cleft lip is a type of clefting congenital deformity caused by abnormal facial development during gestation. It is the non-fusion of the body's natural structures that form before birth. A cleft lip or palate can be successfully treated with surgery, especially so if conducted soon after birth or in early childhood.

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