Identity

Other names: BEX1, DJ79P11.1
HGNC (Hugo): BEX2
Location: Xq22.1

DNA/RNA

Note
There was some confusion in the nomenclature of the human BEX genes. The BEX1 referred in the publications (Quentmeier et al., 2005; Yang et al., 2002) is actually BEX2. BEX2, represented by the Genbank accession number AF220189, was called BEX1 by Yang et al. and others (Quentmeier et al., 2005; Yang et al., 2002).

Later on, Alvarez et al. found that AF220189 is more similar to mouse Bex2 than to mouse Bex1 (74% and 68% identical, respectively) and that its chromosomal localization matches that of mouse Bex2 (Alvarez et al., 2005).

Therefore, AF220189 is considered the human homologue of mouse Bex2, and is human BEX2.

Description
BEX2 encodes a gene belonging to the brain expressed X-linked gene family.
It is a putative tumor suppressor as it is silenced in human glioma (Foltz et al., 2006).

The BEX2 gene contains three exons and each of them encodes part of the coding region.
This is in contrast with BEX1, for which the coding region was encompassed by one single exon.

Transcription
The BEX2 transcript (originally named BEX1 in Yang et al.’s paper) is highly expressed in brain, pancreas, testis, and ovary, but is expressed at lower levels in heart, placenta, liver, kidney, spleen, thymus, prostate, small intestine, colon (no mucus), thyroid, spinal cord, and adrenal gland.

It is not expressed in lung, skeletal muscle, peripheral blood leukocyte, stomach, lymph node, trachea, and bone marrow (Yang et al., 2002).

Protein

Note
BEX2 interacts with LMO2 (LIM domain only 2 (rhombotin-like 1)) (Behrens et al., 2003; Han et al., 2005), a LIM-domain containing transcriptional factor.
The interaction between BEX2 and LMO2 may bind to NSCL2 (NHLH2, nescient helix loop helix 2), a neuronal bHLH protein, to regulate NSCL2-dependent transcriptional activity (Han et al., 2005).

Description
BEX2 has multiple protein isoforms. In one isoform (NP_116010.1), it contains 128 amino acid residues.
Expression
Koo et al. assessed the expression pattern of Bex proteins in several different mouse tissues by western blot analysis (Koo et al., 2004). They used a polyclonal chicken antibody directed against a peptide common to the C-terminal region of mouse Bex1 and -2, which are 87% identical and 90% similar in amino acid sequences. They found that Bex1 and -2 proteins are expressed in mouse whole brain without olfactory bulb, olfactory bulb, olfactory epithelium and at a lower level in the heart, kidney, and liver but, not in the lung (Koo et al., 2004).

Localisation
Nucleus and cytoplasm (Koo et al., 2004).

Function
BEX2 is required for the normal cell cycle progression during G1 in breast cancer cells by regulating cyclin D1 and p21 (Naderi et al., 2010a). BEX2 also protects the breast cancer cells against mitochondrial apoptosis. This process was achieved through the positive regulation of anti-apoptotic member Bcl-2 and the negative regulation of pro-apoptotic members BAD, BAK1 and PUMA (Naderi et al., 2010a).

Homology
Five BEX members have been identified in human. They are BEX1, BEX2, NGFRAP1 (nerve growth factor receptor (TNFRSF16) associated protein 1, BEX3), BEX4, and BEX5. They are all clustered on the X chromosome at Xq22.1-2 (Alvarez et al., 2005).

Mutations
None identified.

Implicated in
Glioma
We showed that BEX1 and BEX2 are candidate tumor suppressor genes in malignant glioma in a genome-wide analysis of epigenetic silencing in gliomas (Foltz et al., 2006). We found that BEX1 and BEX2 were reactivated by trichostatin A (TSA), a histone deacetylase inhibitor, or 5-aza-2'-deoxycytidine (5-AzaC), a DNA methyltransferase inhibitor in glioma cell line T98 and U87, and 10 patient-derived primary glioma cell lines (Foltz et al., 2006). We demonstrated that BEX1 and BEX2's expression were silenced in GBM specimens because of extensive promoter hypermethylation at their promoters. Re-expression of either BEX1 or BEX2 led to increased sensitivity to chemotherapy-induced apoptosis and potent tumor suppressor effects in vitro and in a xenograft mouse model (Foltz et al., 2006). We further showed that BEX1 and BEX2 in GBM cells were down regulated by SOX2, a key gene implicated in maintaining the
stemness of embryonic and adult stem cells (Fang et al., 2011).

Le Mercier et al. showed that decreasing BEX2 expression in Hs683 oligodendrogioma cells increased the survival of Hs683 orthotopic xenograft-bearing mice via modulating genes involved in cancer cell migration, such as MAP2, plexin C1, SWAP70, and integrin beta and impairments of vasculogenic mimicry channel formation in vitro and angiogenesis in vivo (Le Mercier et al., 2009).

**Disease**

Gliomas are the primary cancers derived from glial cells in the brain. It is the most frequent cerebral neoplasias. Astrocytomas are the most common type of gliomas. They are slow-growing, and can be found anywhere in the brain, but most often found in the cerebrum. They can be clinically divided into four grades, with glioblastoma (World Health Organization grade IV) being the most common and aggressive. Oligodendroglomas are a type of glioma originating from the oligodendrocytes of the brain or from a glial precursor cell.

**Breast cancer**

**Note**

Naderi et al. showed that BEX2 protein was overexpressed in approximately 50% of malignant breast tumors compared to only 7% of benign breast samples (Naderi et al., 2012). Furthermore, they showed that BEX2 positive tumors identified a subset of breast cancers with the overexpression of ErbB2 and phosphorylated c-Jun proteins (Naderi et al., 2012). They went on to demonstrate that BEX2 downregulation induced mitochondrial apoptosis and sensitizes breast cancer cells to the pro-apoptotic effects of ceramide, doxorubicin and staurosporine (Naderi et al., 2010a). The role of BEX2 in apoptosis is mediated through the modulation of Bcl-2 protein family - it positively regulates anti-apoptotic member Bcl-2 and negatively regulates pro-apoptotic members BAD, BAK1 and PUMA (Naderi et al., 2010a). BEX2 is also required for the normal cell cycle progression during G1 in breast cancer cells through the regulation of cyclin D1 and p21 (Naderi et al., 2010a). BEX2 overexpression also activates the Bcl-2/NF-kappaB pathway in primary breast tumors (Naderi et al., 2010a). c-Jun and p65/RelA bind to the BEX2 promoter and turn on the expression of BEX2 (Naderi et al., 2010b). Interestingly, BEX2 in turn regulates the phosphorylation/activity of c-Jun and p65/RelA, suggesting that BEX2 is involved in a novel feedback mechanism in breast cancer cells (Naderi et al., 2010b).

**Disease**

Breast cancer forms in the tissues of one or both breasts. It primarily affects women, but can also occur in children and men. It can be a highly curable disease if detected and treated early.

**Acute myeloid leukemia**

**Note**

Acute myeloid leukemia (AML) with mixed lineage leukemia (MLL) was defined by the translocation of the mixed lineage leukemia (MLL) gene, which occurs most frequently in infant acute lymphoblastic leukemia and secondary AML. Quentmeier et al. identified BEX2 (was named BEX1 in the original publication) as over expressed and could be used as candidate gene for the diagnosis of acute myeloid leukemia (AML) with mixed lineage leukemia (MLL) translocations (Quentmeier et al., 2005). Fischer et al. (Fischer et al., 2007) and Röhrs et al. (Röhrs et al., 2009) showed that both the HDAC inhibitor trichostatin A (TSA) and the demethylating agent 5-Aza-2’doxycytidine (Aza) substantially increased the expression of BEX2 mRNA in MLL wild-type (MLLwt) cells, suggesting that BEX2 is an epigenetically regulated gene (Fischer et al., 2007; Röhrs et al., 2009). Röhrs et al. found that MLL fusion proteins seemed to be responsible for the hypomethylation and higher expression of the tumor suppressor gene BEX2 in acute myeloid leukemia (AML) with mixed lineage leukemia (MLL) translocations (Röhrs et al., 2009).

**Disease**

Acute myeloid leukemia (AML), one of the most common types of leukemia among adults, is caused by abnormal growth of the cells that would otherwise normally turn into white blood cells inside the bone marrow. It generally occurs around age 60.

**References**


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Naderi A, Liu J, Bennett IC. BEX2 regulates mitochondrial apoptosis and G1 cell cycle in breast cancer. Int J Cancer. 2010a Apr 1;126(7):1596-610


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