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Gene Section
Review

CRYAB (crystallin, alpha B)

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Identity

Other names: Alpha(B)-crystallin; CRYA2; CTPP2; HSPB5; HspB5

HGNC (Hugo): CRYAB

Location: 11q23.1

DNA/RNA

Description

Crystallins are a highly conserved protein family consisting of three classes, alpha, beta and gamma. The alpha crystallins are divided into two groups according to their acidic as well as basic character, namely A and B. The genes encoding the alpha crystallins A and B are located at chromosome 11 and 21, respectively. The hamster alpha-B crystallin (CRYAB) gene, which is highly homologous to that of humans, was cloned at first by Quax-Jeuken and it was demonstrated that the coding region of CRYAB consists of three exons (Quax-Jeuken et al., 1985).

Transcription

CRYAB was primarily found to be expressed in the lens. At the mRNA level Dubin and his group were the first to detect CRYAB expression in several other tissues such as the lung, heart, skeletal muscle, kidney and to a lower extent within the brain and spleen (Dubin et al., 1989).

Protein

Description

CRYAB encodes a 175 amino acid long protein with a molecular weight of 22kDa. Although the three-dimensional structure of CRYAB has not been resolved yet, the crystal structures of closely related other members of the heat shock protein family are available. This provided the assumption that CRYAB is composed of a highly conserved "alpha crystallin core" domain consisting of about 80 to 100 residues with a beta-sandwich structure (Ghosh et al., 2005).

Expression

CRYAB was initially found in the vertebrate lens. Iwaki and his group demonstrated CRYAB expression within heart, skeletal muscles, striated muscle, sciatic nerve, kidney and placenta by immunohistochemistry as well as immunoblotting and northern analyses (Iwaki et al., 1990). Further-more, CRYAB was found to be expressed in several human neoplasms.

Localisation

CRYAB exhibits mainly a cytosolic distribution. However, nuclear localisation with speckled intra-nuclear formations in various types of unstressed cells was also reported (van den et al., 2003).

Function

CRYAB as well as alpha-A crystallin contribute to ~35% of all vertebrate lens proteins. Therefore, it was firstly suggested that these proteins might be responsible for the refractory index of the eye and for maintaining lens transparency. However, the high abundance of CRYAB in tissues other than the lens and its high homology to heat shock proteins suggested that CRYAB might also represent a small heat shock protein with the potential to exert molecular chaperone function. This suggestion was strengthened by Klemenz et al. by showing heat shock inducability of CRYAB on the promoter level (Klemenz et al., 1991). Basing on the potential of heat shock proteins to bind to

unfolded and denatured proteins, thus maintaining a less non-specific protein aggregation, a potential role of CRYAB in inclusion body formation in the course of several neurodegenerative diseases such as Alexander disease (Iwaki et al., 1993), Alzheimer's disease (Shinohara et al., 1993), Creutzfeldt-Jacob disease (Kato et al., 1992) and Parkinson's disease (Iwaki et al., 1992) has been suggested. Further-more CRYAB was found to serve as an auto-antigen in multiple sclerosis (van Noort et al., 1995) and it was shown that small heat shock proteins such as CRYAB are involved in the promotion of prolonged survival of cancer cells by inhibiting apoptosis (Kamradt et al., 2001).

Homology

CRYAB exhibits a high homology of 56% to alpha-A-crystallin. Moreover, additional homologies to several other heat shock proteins were demonst-rated (Wistow, 1985).

Mutations

Note

Until now, there are two known mutations within the CRYAB gene with potential impact on human pathologies. Vicart and his group found a missense mutation of R120G within the CRYAB gene, which was associated with desmin-related myopathy (Vicart et al., 1998). Furthermore a deletion muta-tion within exon 3, 450delA, which results in an aberrant protein, was found to be related to dominant posterior congenital cataract in humans (Berry et al., 2001).

Implicated in

Breast cancer

Note

It was reported that CRYAB expression is strongly associated with lymph node metastasis in breast cancer (Chelouche-Lev et al., 2004). This result was further supported by the high abundance of CRYAB in basal like breast carcinoma, which represents a subgroup of breast cancers with bad prognosis and high metastatic potential (Moyano et al., 2006). Furthermore, this research group demonstrated activation of the MEK/ERK pathway through CRYAB over-expression in immortalized human mammary epithelial cells, which lead to increased cell migration and invasion. This effect could be entirely suppressed using MEK/ERK inhibitors.

Renal cell carcinoma

Note

Up-regulation of CRYAB expression was found in cultured renal cell carcinoma cells as well as in tissues derived from renal cell carcinomas (Shi et al., 2004). This finding was further confirmed by another research group using protein chip and immunohistochemistry analyses (Holcakova et al., 2008).

Brain tumours

Note

Expression of CRYAB within malignant brain tumours such as astrocytomas, oligodendrogliomas and glioblastoma multiforme (GBM) was reported (Iwaki et al., 1991; Aoyama et al., 1993; Shinohara et al., 1993). Moreover, it was demonstrated that chemotherapy induces an increased expression of CRYAB in neuroblastomas (Ishiguro et al., 1997). Comparative proteomic studies on human low grade astrocytomas and GBM showed a significant higher expression of CRYAB within the GBM (Odreman et al., 2005).

Anaplastic thyroid carcinoma

Note

Mineva showed differential regulation of CRYAB and the closely related heat shock protein 27-1 (HSP27-1) within the highly malignant anaplastic thyroid carcinomas (ATC). Whereas CRYAB expression was found to be down-regulated, HSP27-1 was considerably expressed within ATC (Mineva et al., 2005). Analyses of the CRYAB promotor region including tumor associated methylation analysis as well as CRYAB promoter specific trasncription factor analysis lead to the suggestion that this might be due to tumor specific transcription factor and promoter methylation patterns.

Buccal squamous carcinoma

Note

This type of carcinoma, which is mostly seen in central and southeast Asia, is characterized by a considerably aggressive course. Chen and his group performed a proteomic assay in order to define the expression pattern of cancer-related proteins within this tumor entity. Similar to the anaplastic thyroid carcinomas, CRYAB was found to be under-represented, whereas several other proteins involved in heat shock responses and anti-oxidative processes were up-regulated (Chen et al., 2004).

Head and neck cancer

Note

In consistence with findings of breast cancer research, a high extent of CRYAB expression was found to be a strong predictive marker for short survival rates of patients suffering from head and neck cancer (Chin et al., 2005). However, an investigation of head and neck squamous cell carcinoma did not reveal a significant association between patient survival and CRYAB expression (Boslooper et al., 2008).

Hepatocellular carcinoma

Note

The CRYAB gene was found to be highly expressed in a subgroup of hepatocellular carcinomas, which was

associated with declined survival rates (Tang et al., 2009). It was suggested that CRYAB might serve as a prognostic marker within hepatocellular carcinomas.

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