Expression

The expression patterns of Cthrc1 during murine embryonic development and in postnatal tissues have been characterized with in situ hybridization and immunohistochemistry (see Durmus et al., 2007 for a complete review). Cthrc1 expression levels are induced in the adventitia and intimal smooth muscle after balloon catheter injury of arteries. Additionally, Cthrc1 is highly expressed in cartilage and developing bones as well as in myofibroblasts during skin wound healing. Indirect evidence for the expression of Cthrc1 by hair cells of the inner ear has been reported in a Cthrc1 mutant mouse with a beta-galactosidase expression construct replacing the first exon of Cthrc1. Expression of Cthrc1 is increased in fibroblasts and chondrocytic cells in response to TGF-beta family members including BMP4, BMP2 and TGF-beta. Cthrc1 is also upregulated during tumorigenesis and metastasis; its role during this process is unknown.

Localisation

Cthrc1 has a signal peptide that targets it to the ER-Golgi pathway for secretion. In the extracellular environment the molecule is sensitive to cleavage by proteases such as plasmin. While CTHRC1 is abundant in cartilage matrix, the CTHRC1 protein has been observed in the cytoplasm of select cell types such as certain neuronal populations and parafollicular cells of the thyroid gland despite the presence of the signal peptide.

Function

Cthrc1 has been linked to major signaling pathways such as Wnt and TGF-beta. The ability of CTHRC1 to inhibit TGF-beta signaling via a reduction in Smad 2/Smad 3 phosphorylation has been demonstrated both in vivo and in vitro models. This inhibition translates into a reduction in collagen type I deposition during vascular remodeling. Characterization of Cthrc1 deficient mice indicated that the gene is not essential for normal development. Evidence from in vitro studies suggested that Cthrc1 may play a role in the Planar Cell Polarity (PCP) pathway of non-canonical Wnt signaling. Combinatorial mutations in both Cthrc1 alleles and a single allele of Vangl2, a gene previously shown to be involved in noncanonical Wnt signaling, resulted in animals lacking proper orientation of inner and outer ear hair cells. Further biochemical analysis showed
Cthrc1 associated with several of the Frizzled family of receptors suggesting it may stabilize the receptor ligand complex on the cell surface. Cthrc1 deficient mice also demonstrated a reduction in bone density that was attributable to a reduction in osteoblast number and coverage. Mechanistically, it is unclear how this occurs but was shown to be due to a reduction in osteoblast proliferation rather than an increase in osteoclasts.

**Homology**

Cthrc1 is a unique protein, displaying an extremely high level of conservation among vertebrates, but showing very little homology to other currently known proteins. Structurally, it contains a short collagen-like motif similar to the collagen domains present in the C1q/tumor necrosis factor-a-related proteins (CTRPs). Both CTHRC1 and CTRP members share a conserved and post-translationally modified lysine residue present in the collagen domain, but currently there are no data to suggest that the collagen domain of CTHRC1 leads to trimerization.

**Implicated in**

**Breast cancer**

**Disease**
Lobular carcinoma and invasive ductal carcinoma.

**Prognosis**
Undetermined. Suggested that CTHRC1 expression in these tumors is associated with cancer tissue invasion and metastasis.

**Solid cancers**

**Disease**
Melanomas, cancers of the rectum, small intestine, colon, liver, lung, ovary, breast, thyroid gland and cervix.

**Prognosis**
Cthrc1 is upregulated in solid tumors. Linked expression levels to prognosis is undetermined.

**References**


*This article should be referenced as such:*