

Gene Section

Review

BTRC (beta-transducin repeat containing)

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Identity

Other names: BETA-TRCP; BTRCP; E3RSIkappaB; FBW1A; FBXW1; FBXW1A; FWD1; Fwd1; MGC4643; bTrCP; bTrCP1; beta-TrCP1; betaTrCP

HGNC (Hugo): BTRC

Location: 10q24.32

DNA/RNA

Description

Spans 223.25 kb; 14 exons; 13 coding exons (Figure 1).

Transcription

Full length transcript of 6011 bp, open reading frame 1707 bp. There is an alternatively spliced transcript (Figure 1).

Protein

Description

There are two isoforms of betaTrCP1; isoform 1 consists of 569 amino acid residues and isoform 2 comprises 605 amino acid residues. Both isoforms contain an F-box domain and seven WD40 repeats, which bind SKP1 and protein substrates, respectively. Their function is indistinguishable (Figure 2).

Expression

BetaTrCP1 is expressed in the majority of human tissues with high levels in the brain, heart, and testis, but undetectable levels in the small intestine and thymus (Cenciarelli et al., 1999).

Localisation

betaTrCP1 protein is predominantly localized in the nucleus, while betaTrCP2 is primarily found in the cytoplasm (Cenciarelli et al., 1999; Lassot et al., 2001; Davis et al., 2002).

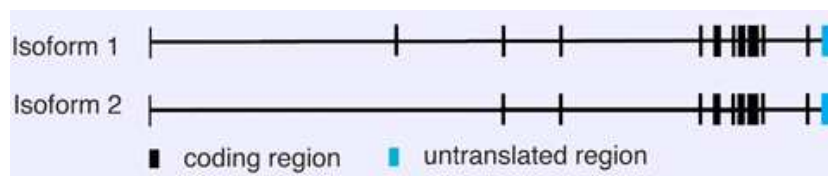


Figure 1. The betaTrCP1 gene structure.

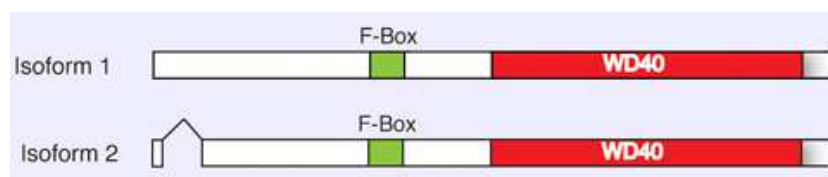


Figure 2. Two isoforms of betaTrCP1 protein.

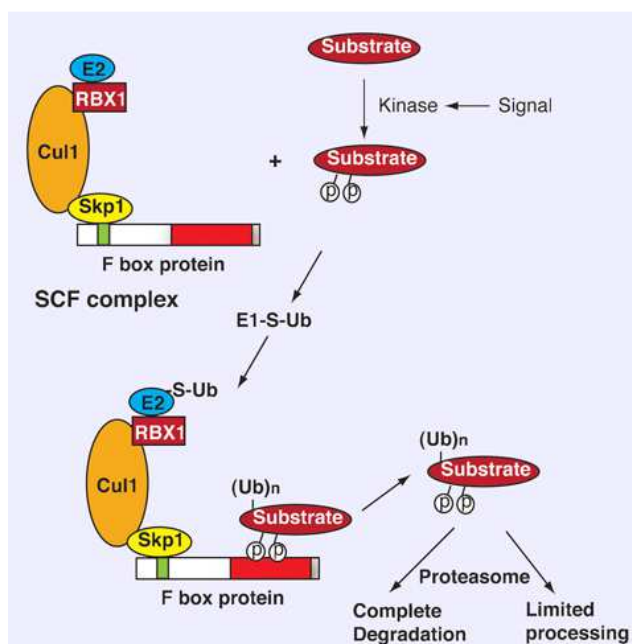


Figure 3. Diagrammatic drawing showing the SCF complex and how it recognizes its substrate for degradation by the proteasome. (Ub)_n, polyubiquitin; P, phosphate group; E1 and E2, ubiquitin E1 and E2 enzymes; Cul1, RBX1, Skp1, and F box protein, SCF components.

Function

BetaTrCP1 is a member of the F-box proteins. Sixty nine F-box proteins have been identified in humans, and they are classified into three groups: those with WD40 domains (FBXWs), those with leucine-rich repeats (FBXLs), and those with other diverse domains (FBXOs) (Cenciarelli et al., 1999; Winston et al., 1999a; Jin et al., 2004). BetaTrCP1 is the substrate recognition subunit, which together with SKP1, Cullin1, and RBX1 (also known as ROC1), makes up the SCF (SKP1-CUL-F-box protein) complex or E3 ubiquitin ligase. BetaTrCP1 recognizes a DSGXXS destruction motif in which the serine residues are phosphorylated by specific kinases (Fig. 3). It also binds the variants of this motif where acidic residues substitute for phosphorylated serine residues (Frescas and Pagano, 2008). The binding of BTrCP results in ubiquitination and subsequent degradation of its substrates by the proteasome (Fig. 3).

Targets of the SCF ubiquitin ligase can be divided into two main groups on the basis of their function: cell cycle regulators and transcription factors. They include: IKappaB (Yaron et al., 1998; Hatakeyama et al., 1999; Kroll et al., 1999; Shirane et al., 1999; Spencer et al., 1999; Tan et al., 1999; Winston et al., 1999b; Wu and Ghosh, 1999), NFkappaB (Orion et al., 2000; Fong and Sun, 2002; Lang et al., 2003; Amir et al., 2004), beta-catenin (Kitagawa et al., 1999; Winston et al., 1999b), GLI2 (Huntzicker et al., 2006; Pan et al., 2006), GLI3 (Wang and Li, 2006; Tempe et al., 2006), REST (Guardavaccaro et al., 2008; Westbrook et al., 2008), ATF4 (Lassot et al., 2001), PER1/PER2 (Eide et al., 2005; Shirogane et al., 2005; Reischl et al., 2007), VPU (Besnard-Guerin et al., 2004), Claspin (Peschiaroli et

al., 2006; Mailand et al., 2006), Emi1 (Guardavaccaro et al., 2003), CDC25A (Busino et al., 2003; Kanemori et al., 2005), CDC25B (Kanemori et al., 2005), WEE1 (Watanabe et al., 2004), MLC1 (Ding et al., 2007), etc. Among these targets, NFkappaB, GLI2, and GLI3 are degraded in a limited fashion instead of completely (Fig. 3).

Homology

BetaTrCP1 is paralogous to betaTrCP2 (also termed HOS or Fbw1b) (Fuchs et al., 1999; Suzuki et al., 2000; Bhatia et al., 2002); the two are collectively called BTrCP, as their biochemical properties are indistinguishable. BTrCP is homologous to Slimb in *Drosophila*, which targets Armidillo (the B-catenin homolog) and Ci (the homolog of Gli) for degradation, though limited for the latter (Jiang and Struhl, 1998; Jia et al., 2005; Smelkinson and Kalderon, 2006; Smelkinson et al., 2007).

Mutations

Note

Mutations in BTrCP in both germinal and somatic cells are rarely found in human tumors, probably because of the redundancy of the two BTrCP paralogues.

Implicated in

Various Cancer

Oncogenesis

Overwhelming evidence indicates that BTrCP mostly displays an oncogenic activity. Two point mutations in betaTrCP1 have been found from 22 prostate cancer samples (Gerstein et al., 2002). Five missense

mutations have also been identified in 95 gastric cancers (Kim et al., 2007). In addition, an in-frame deletion of three amino acid residues in betaTrCP2 has been detected in breast cancers in a large scale genomic DNA sequencing project (Wood et al., 2007). However, it is not clear whether these mutations causally associate with tumorigenesis, as the function of these mutated BTRCP gene products has not been determined. On the other hand, it has been well established that overexpression of bTrCP proteins is associated with several types of human tumors, including colorectal cancers (Ougolkov et al., 2004), pancreatic cancers (Muerkoster et al., 2005), and breast cancers (Spiegelman et al., 2002), melanoma (Dhawan and Richmond, 2002; Liu et al., 2007), and hepatoblastomas (Koch et al., 2005). In most of these tumors, overexpression of BTRCP results in the degradation of IkappaB, an inhibitor for the NFkappaB transcription factor, and thus the activation of NFkappaB. In others, the increased BTRCP expression also correlates with the activation of beta-catenin, the transcription regulator for WNT signaling. Therefore, it is believed that the activation of either NFkappaB, beta-catenin, or both is the main mechanism by which the upregulated BTRCP expression results in uncontrolled cell proliferation in these tumors.

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