BCL2L15 (BCL2-like 15)

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Identity

Other names: Bfk, C1orf178, FLJ22588
HGNC (Hugo): BCL2L15
Location: 1p13.2
Local order: Centromere to telomere.

DNA/RNA

Description

The BCI2L15 gene has a total length of 10734 nt and consists of 4 exons and 3 intervening introns (Coulta et al., 2003). The organization of the BCL2L15 gene, with the BH3 domain located on a single exon (exon 2) and the BH2 domain split between two exons (exons 3 and 4), is similar to that of other BCL2 family members, including BCL2, BCL2L1 (BCLX), BAX, and BAK1 (BAK) (Petros et al., 2004).

Figure 1. Schematic representation of the BCL2L15 gene. Exons are shown as boxes and introns as connecting lines. The coding sequences are highlighted as red, while 5' and 3' untranslated regions (UTRs) are shown in white. Numbers inside or outside boxes indicate lengths (nt) of exons and introns, respectively, while numbers in parentheses indicate lengths (aa) of protein isoforms. Arrows (↓) show the position of the start codons (ATG) and asterisks (*) denote the position of the stop codons (TGA). Question marks (?) indicate that the full-length sequence was not determined. Roman numerals indicate intron phases. The intron phase refers to the location of the intron within the codon; I denotes that the intron occurs after the first nucleotide of the codon, II denotes that the intron occurs after the second nucleotide, and 0 means that the intron occurs between distinct codons. The figure is drawn to scale, except for the introns containing the (//) symbol.
Transcription

The BCL2L15 gene is subjected to alternative splicing, generating four splice variants, three of which are considered as coding transcripts. Each coding splice variant consists of a distinctive exon combination and encodes a different protein isoform. The predominant transcript, consisting of 4973 nt, includes all 4 exons and encodes isoform a. The second transcript, predicted to encode isoform b, contains exons 1, 2 and 4. The deletion of exon 3 does not result in frameshifting. The third transcript, putatively encoding isoform d, consists of exons 1 and 4. The lack of exons 2 and 3 shifts the open reading frame.

As aforementioned, except for alternatively spliced BCL2L15 coding variants, another noncoding transcript has also been identified. This one is composed of exons 1, 3 and 4, and was initially considered to encode isoform c. Nonetheless, this transcript is a nonsense-mediated mRNA decay (NMD) candidate, since deletion of exon 2 generates a premature translation termination codon in exon 3.

Interestingly, transcription of all BCL2L15 alternatively spliced variants was noticed only in colon, while the full-length transcript was also detected in stomach, rectum, small intestine, cerebellum, testis and uterus (Dempsey et al., 2005). Moreover, despite the fact that a p53 consensus binding site was identified upstream of the transcription initiation site of BCL2L15, this gene does not constitute a transcriptional target of p53 (TP53) (Ozören et al., 2009).

Pseudogene

Not identified so far.

Protein

Description

The full-length BCL2L15 isoform (isoform a) is the predominant one. It consists of 163 amino acid residues and has a molecular mass of 17.7 kDa. BCL2L15 isoform a contains a BH3 and a BH2 domain, but no BH1, BH4 or hydrophobic tail (Coultas et al., 2003). Isoform a is the predominant BCL2L15 isoform and the only one that has been in vivo detected so far.

The amino acid sequences of isoforms b and c are deduced from the mRNA sequences of the BCL2L15 alternatively spliced variants, and remain to be experimentally validated and in vivo detected. Isoform b is a putative BH3-only protein of 88 amino acid residues, with a calculated molecular mass of 9.6 kDa. This isoform shares the same termini with BCL2L15 isoform; still, it bears no BH2 domain. Finally, isoform d is the smallest predicted BCL2L15 isoform. This protein of 56 amino acid residues, with a molecular mass of 6.3 kDa, possesses no BCL2-homology (BH) domains (Dempsey et al., 2005). The N-terminal region of all BCL2L15 isoforms shares partial homology (ECIxNxLxxxFL peptide) with BID (Dempsey et al., 2005), a BH3-only proapoptotic member of the BCL2 family (Lomonosova and Chinnadurai, 2008). Moreover, all BCL2L15 isoforms contain a caspase-3/caspase-7 cleavage site (DEVD peptide) (Dempsey et al., 2005). This tetrapeptide, corresponding to amino acid residues 38-41, is responsible for the removal of an N-terminal peptide fragment and the subsequent activation of the predominant BCL2L15 isoform, at least during DNA damage-induced apoptosis (Dempsey et al., 2005; Ozören et al., 2009).

Figure 2. Alignment of amino acid sequences and structural motifs of the BCL2L15 protein isoforms. Light blue and pink denote the BH2 and BH3 domains, respectively, while the amino acid residues constituting the consensus sequence of each BCL2 homology domain are shown in dark blue and red color. Yellow highlights the site of caspase-3/7 cleavage (DEVD tetrapeptide), which is considered to be critical for the activation of the proapoptotic action of BCL2L15, at least in certain cell types and/or after certain stimuli, including DNA damage-induced apoptosis. Finally, light green highlights the ECIxNxLxxxFL peptide, which BCL2L15 isoforms share with BID; its conserved amino acid residues are shown in dark green.
Expression

The BCL2L15 protein is mainly expressed in tissues of the gastrointestinal tract, including the stomach, small intestine, colon and rectum (Dempsey et al., 2005; Ozören et al., 2009). The full-length isoform has also been detected in several colorectal cancer cell lines, such as SW480, HT-29 and HCT116 (Ozören et al., 2009).

Localisation

The BCL2L15 protein is localized to the cytoplasm of intestinal epithelial cells (Ozören et al., 2009). It does not possess any signal peptide or C-terminal membrane anchor and, consequently, it is not associated with any cellular organelles (Coultas et al., 2003; Ozören et al., 2009), unlike other members of the BCL2 family (Thomadaki and Scorilas, 2006). The localization of the cleaved BCL2L15 has not been elucidated yet.

Function

BCL2L15 is a weakly proapoptotic member of the BCL2 family (Coultas et al., 2003; Dempsey et al., 2005; Pujianto et al., 2007). When overexpressed, the full-length BCL2L15 isoform interacts with BCL2L1 long isoform (BCLXL) and BCL2L2 (BCLW), but not with BCL2 or BAD, as revealed by co-immunoprecipitation experiments (Ozören et al., 2009). Furthermore, it has been speculated that BCL2L15 acts most probably as an amplifier of the apoptotic signal rather than a trigger of programmed cell death (Pujianto et al., 2007; Ozören et al., 2009).

Given the weak proapoptotic activity of BCL2L15, it was initially suggested that the full-length BCL2L15 could represent the latent form of a potent BH3-only protein exerting its proapoptotic action once activated through proteolytic cleavage (Coultas et al., 2003), like caspase-8 cleavage of BID (Li et al., 1998; Luo et al., 1998), at least in certain cell types or after certain stimuli. In support of this notion, it was shown that BCL2L15 becomes cleaved in a caspase-dependent manner during DNA damage-induced apoptosis and that truncated BCL2L15 (~13 kDa), corresponding to the part of protein downstream of the caspase-3/7 cleavage site, is capable of inducing apoptosis in HCT116 cells, in contrast to the full-length BCL2L15 isoform, which seems to be incapable of inducing apoptosis in HCT116 or SW480 colorectal cancer cells. Interestingly, the ability of the cleaved form of the BCL2L15 protein to induce apoptosis is dependent on the presence of the BAX or BAK1 (BAK). Furthermore, co-expression of the antiapoptotic BCL2L1 long isoform (BCLXL) or BCL2L2 (BCLW) antagonizes efficiently the killing activity of truncated BCL2L15 (Ozören et al., 2009).

On the other hand, it has been proposed that the proapoptotic role of BCL2L15 may resemble more that of BAX and BAK1 (BAK) than that of BH3-only proteins, since it most probably has a structure similar to that of BCL2 and BAX. In fact, the position of BH3 and BH2 domains in the BCL2L15 protein is conserved relative to BAX and BCL2 (Coultas et al., 2003). Potential phosphorylation at Ser-96 and/or Ser-42 as well as other post-translational modifications of BCL2L15 might change its subcellular localization and further regulate its physiological function (Dempsey et al., 2005; Pujianto et al., 2007).

Homology

Human BCL2L15 shares 71% amino acid identity and 80% similarity with the mouse ortholog. BCL2L15 bears the same combination of BCL2-homology domains (BH2 and BH3) as the BCL2L14 long isoform (BCLGL) and BCL2L12 full-length isoform, thus lacking other domains that are common among BCL2 family members (BH1 and BH4) or a hydrophobic tail (Youle and Strasser, 2008).

Mutations

Note

A single nucleotide polymorphism (SNP) has been detected in the coding sequence (GAC→AAC) of the BCL2L15 gene, which results in the substitution of an amino acid residue bearing a negatively charged side chain by an amino acid with a polar uncharged side chain (D→N).

Implicated in

Gastrointestinal cancer, particularly colorectal carcinoma

Prognosis

BCL2L15 mRNA expression is clearly reduced in a wide range of gastrointestinal malignancies. BCL2L15 mRNA levels are lower in colon tumors, compared to levels detected in matched normal colon tissue. Moreover, BCL2L15 mRNA expression is significantly downregulated in tumors of the small intestine, stomach and rectum. This reduction of BCL2L15 mRNA levels in gastrointestinal neoplasms implies that BCL2L15 may contribute to the protective effect of proapoptotic BCL2 family proteins against malignant transformation of the gastrointestinal tract (Dempsey et al., 2005).

References


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