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Gene Section
Review

BCL2L15 (BCL2-like 15)

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Abstract

This review collects the data on DNA/RNA, the protein encoded and the diseases where BCL2L15 is involved.

Identity

Other names: BFK, C1orf178

HGNC (Hugo): BCL2L15

Location: 1p13.2

Local order: Centromere to telomere.

DNA/RNA

Description

The BCl2L15 gene has a total length of 10766 nt and consists of 4 exons and 3 intervening introns (Coultas 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).

Transcription

The BCL2L15 gene is subjected to alternative splicing, generating seven 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 (v. a; Genbank accession number: NM_001010922.3), consisting of 5005nt, includes all 4 exons and encodes isoform 1. The second transcript (v. b; Ensembl accession number: ENST00000471267.1), predicted to encode isoform 2, contains exons 1, 2 and 4. The deletion of exon 3 does not result in frameshifting. The third transcript (v. d; Ensembl accession number: ENST00000393320.3), probably encoding isoform 3, consists of exons 1 and 4. Skipping of exons 2 and 3 leads to open reading frame shifting.
Another transcript has also been identified (v. c; Ensembl accession number: ENST00000464132.1). This one is composed of exons 1, 3 and 4, and was initially considered to encode a small, non-functional isoform c, which did not contain any BH domains. Nonetheless, the in silico analysis revealed that this transcript is, probably, 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 TP53 consensus binding site was identified upstream of the transcription initiation site of BCL2L15, this gene does not constitute a transcriptional target of p53 (TP53) (Ozoren et al., 2009).

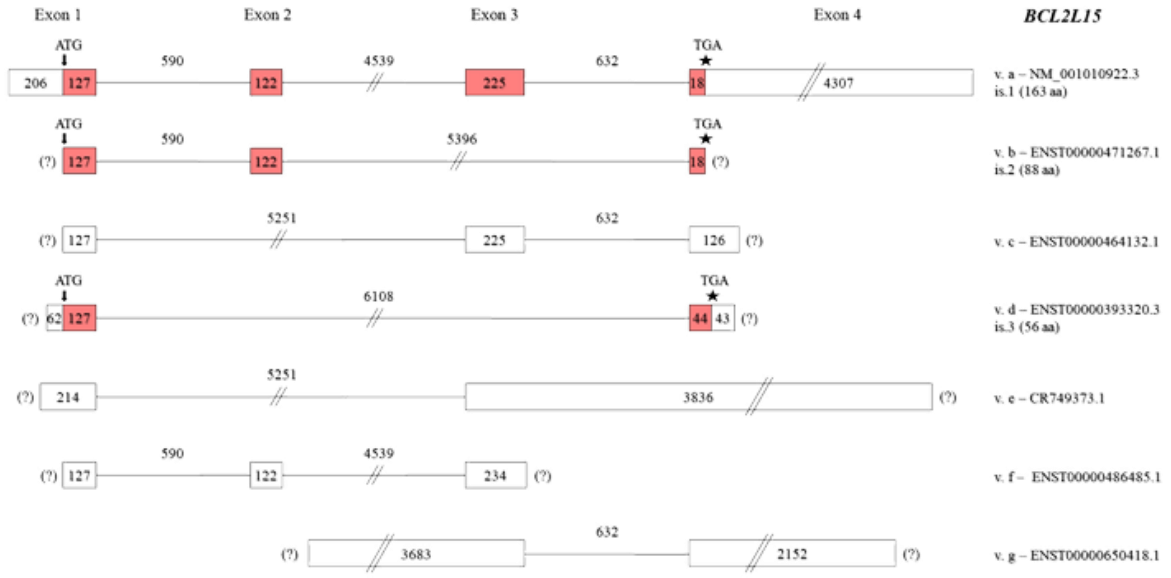

Figure 1. Schematic representation of the human BCL2L15 gene. Exons are shown as boxes and introns as connecting lines. The coding sequences are highlighted as red, while 5' and 3' untranslated regions (UTRs) are shown colorless. Numbers inside or outside boxes indicate lengths (nt) of exons and introns, 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. The figure is drawn to scale, except for the introns containing the (//) symbol.

In addition to the aforementioned four transcripts, there are three additional splice variants (Genbank accession number: CR749373.1; Ensembl accession numbers: ENST00000486485.1 and ENST00000650418.1), which to the best of our knowledge are not mentioned in any research study, yet their partial sequences have been deposited in publicly available databases.

Pseudogene

Not identified so far.

Protein

Description

The full-length BCL2L15 isoform (isoform 1) is the predominant one and the only one that has been experimentally identified in vivo, so far. 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).

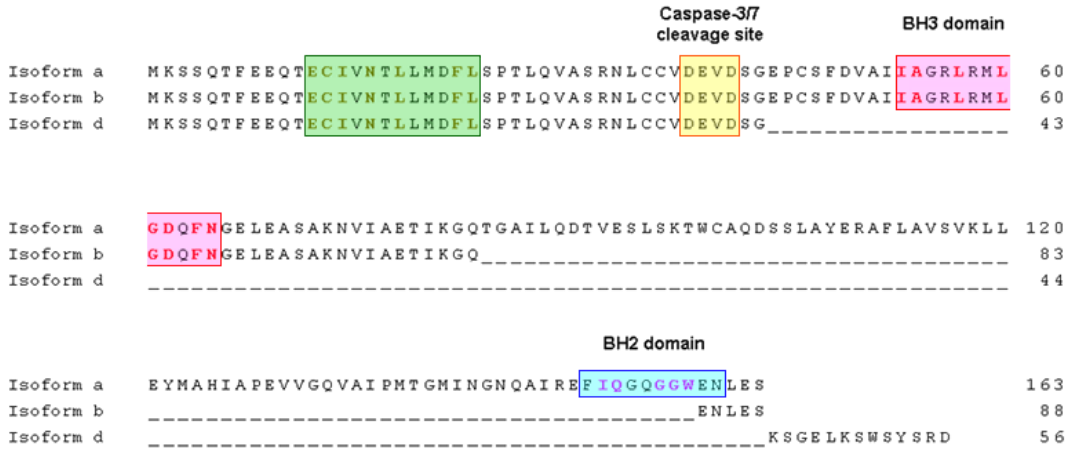

Figure 2. Alignment of amino acid sequences and structural motifs of the human BC2L15 protein isoforms. Light blue and pink denote the BH2 and BH3 domains, respectively, while the amino acid residues constituting the consensus sequence of each BCL2 homology domain are shown in dark blue and red color. 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.

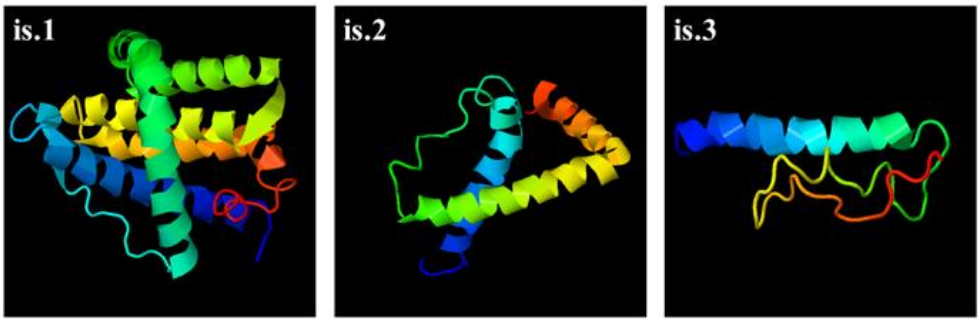

Figure 3. Predicted models of the precursors of the BCL2L15 protein isoforms. The 3D structures were predicted using the I-TASSER server (Yang and Zhang, 2015). For each protein, only the 3D structure with the highest confidence score is presented. The RasMol 'Group' color scheme color codes residues by their position in a macromolecular chain. Each protein is drawn as a smooth spectrum from blue through green, yellow and orange to red. Thus, the N-termini are colored blue and the C-termini are drawn in red

A pseudo-BH1 domain has, also, been detected, in which only some of the critical amino acids remain conserved (Ozoren et al., 2009).

The amino acid sequences of isoforms 2 and 3 are deduced from the mRNA sequences of the BCL2L15 alternatively spliced variants, and remain to be experimentally validated and in vivo detected.

Isoform 2 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). This feature is in accordance with the decreased proapoptotic function of this isoform.

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). The fact that all three isoforms comprise this peptide highlights its potential significance regarding BCL2L15 function. Moreover, all BCL2L15 isoforms contain a caspase-3/7 (CASP3 and CASP7) cleavage site (DEVD peptide), similar to BID (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; Ozoren et al., 2009).

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; Ozoren et al., 2009). The full-length isoform has also been detected in several colorectal cancer cell lines, such as SW480, HT-29 and HCT116 (Ozoren et al., 2009). Additionally, low levels of the BCL2L15 protein have also been detected in a variety of tissues including oesophagus, gallbladder, liver, bone marrow, and lymphoid tissues, as shown in 'The Human Protein Atlas' database. The murine ortholog has increased expression in epididymis and in the epithelium of pregnant female mammary gland (Pujianto et al., 2007).

Localisation

The BCL2L15 protein is localized to the cytoplasm of intestinal epithelial cells (Ozoren 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; Ozoren et al., 2009), unlike other members of the BCL2 family (Thomadaki and Scorilas, 2006). However, according to Gene Ontology analysis, it may also be localized in the nucleus, while there are also indications regarding its localization to other cellular organelles and to the cytoskeleton (Gaudet et al., 2011). The nucleus localization has also been validated in the mouse, where the predominant expression of Bcl2l15 murine ortholog was demonstrated. This discrepancy in Bcl2l15 localization could be attributed to cell-specific posttranslational modifications which lead to its alternation (Pujianto et al., 2007). 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). Initially, it was believed that BCL2L15 was unable to bind to other BCL2 family proteins and regulate their function, despite the presence of the BH3 domain. This was observed for the murine ortholog.

Due to the fact that BCL2L13 has the same feature, it was implied that these two proteins may belong to the same family (Coultas et al., 2003). However, additional co-immunoprecipitation experiments

revealed that the full-length BCL2L15 protein isoform interacts with BCL2L1 long isoform (BCLXL) and BCL2L2 (BCLW), but not with BCL2 or BAD (Ozoren 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 (Ozoren et al., 2009; Pujianto et al., 2007).

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 (CASP8) 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 (CASP3 and CASP7) 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 (Ozoren 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).

Interestingly, Bcl2l15 expression has also been detected in mouse, particularly in the initial segment of epididymis, proposing a potential role in the differentiation of this particular segment. In the same research study, it was suggested that Bcl2l15 exerts its proapoptotic function only following apoptosis initiation. This finding, combined with the fact that Bcl2l15 expression is regulated by androgens and other testicular factors, supports the notion that the role of Bcl2l15 in epididymis is the epithelial proliferation and differentiation rather than triggering apoptosis (Pujianto et al., 2007). Additionally, elevated expression of Bcl2l15 has been observed during pregnancy, as well. However, its physiological function necessitates further elucidation (Coultas et al., 2003).

Due to the high amino acid identity and similarity between human and mouse orthologs, it would be interesting if the aforementioned potential functions of Bcl2l15 were investigated in human, as well. This analysis could help the clarification of the role of BCL2L15 and uncover hidden aspects of its function. However, it should be taken into consideration that these two orthologs have particular differences which could affect their tissue specificity or distribution, such as the lack of the DEVD peptide in the mouse ortholog.

Homology

Human BCL2L15 shares 69% 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 full-length BCL2L12 isoform, thus lacking other domains that are common among BCL2 family members (BH1 and BH4) or a hydrophobic tail (Youle and Strasser, 2008).

Mutations

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) (Gerhard et al., 2004; Ota et al., 2004).

Implicated in

Gastrointestinal cancer

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).

A recent research study correlates BCL2L15 with the transcription factor PROX1 in the context of abnormally activated Wnt pathway in colorectal cancer, highlighting that BCL2L15 is a direct target of PROX1. More specifically, the suppression of proapoptotic BCL2L15 protein isoform expression

leads to increased survival rate of PROX1-positive cancer cells undergoing metabolic stress (Ragusa et al., 2014). Additionally, miR-144 was reported to be involved in the mechanism of proliferation and migration of colorectal cancer. Indicatively, it was experimentally proved that MIR144 targets GSPT1, which subsequently is involved in BCL2L15 expression regulation (Xiao et al., 2015). These findings designate the potential multifaced role of BCL2L15 in pathogenesis and metastasis of colorectal cancer.

Endometrial Cancer

Prognosis

Following the analysis of 541 samples of patients with endometrial cancer, it was revealed that high BCL2L15 expression is probably associated with favorable prognosis. The data are derived from 'The Human Protein Atlas', in which a description of each patient and the expression level of BCL2L15 in each case are mentioned. To the best of our knowledge, there is no current research study which investigates the potential role of BCL2L15 in endometrial cancer.

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