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Gene Section
Review

CFLAR (CASP8 and FADD-like apoptosis regulator)

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Identity

Other names: CASH; CASP8AP1; CLARP; Casper; FLAME; FLAME-1; FLAME1; FLIP; I-FLICE; MRIT; USURPIN; c-FLIP; c-FLIPL; c-FLIPR; c-FLIPS

HGNC (Hugo): CFLAR

Location: 2q33.1

DNA/RNA

Description

14 exons; DNA size 48 kb.

Transcription

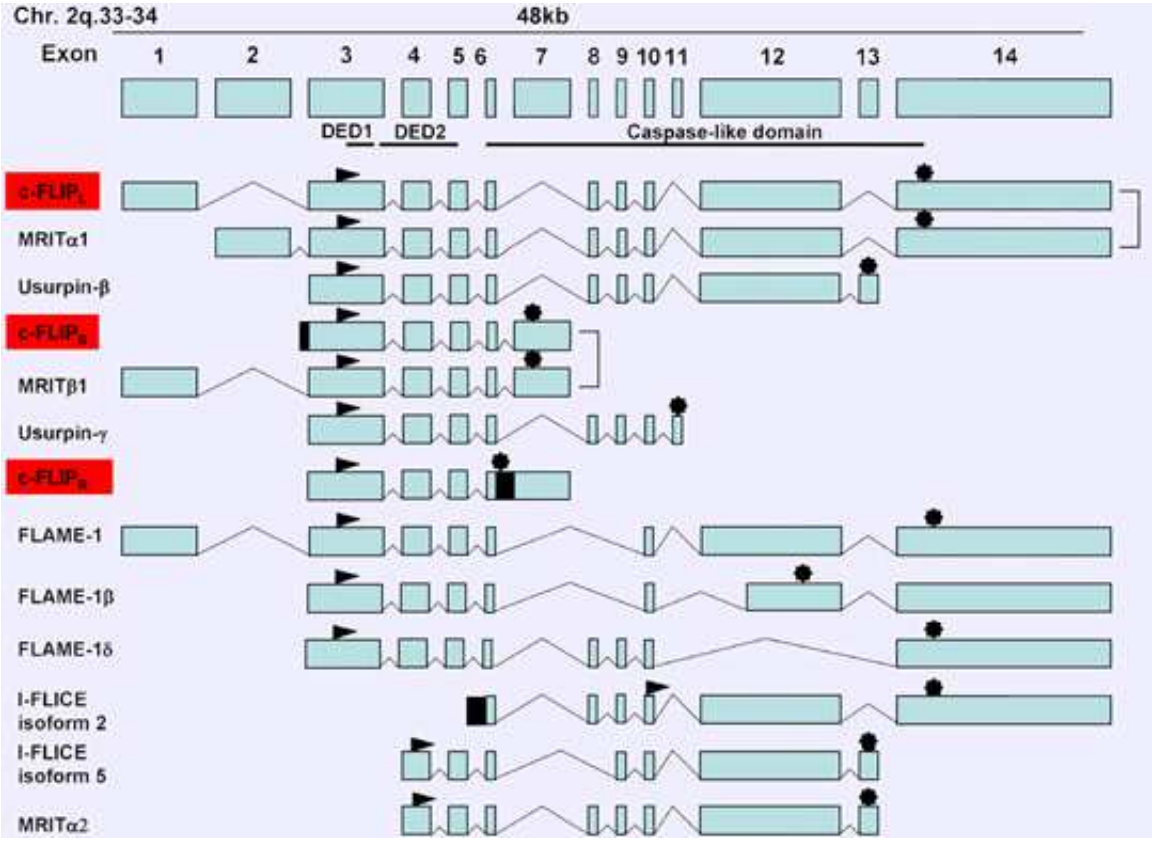
FLIPL: mRNA size: 2243 nucleotides (nt); coding sequence: 1443 nt; FLIPS: mRNA size: 1062 nt; coding sequence: 666 nt.

Protein

Note

In 1997, a new family of viral genes encoding viral FLIP (v-FLIP, Fas-associated death domain (FADD)-like interleukin-1 beta converting enzyme (FLICE) inhibitory protein) were identified as proteins containing the Death Effector Domain (DED) which interact with certain caspases: caspase 8 (also termed FLICE) and caspase 10 (Hofmann, 1999). These proteins are principally composed of two homologous DED regions, which are found in a wide family of DED-containing proteins, including procaspase-8, procaspase-10 and FADD, which are components of the DISC (Death Inducing Signalling Complex) formed by death receptors such as Fas (CD95), DR4 (TRAIL-R1) and DR5 (TRAIL-R2) (Ashkenazi and Dixit, 1999). The v-FLIP proteins were first identified in gamma-herpesviruses, such as the Kaposi-associated human herpesvirus-8 (HHV-8), the equine herpesvirus-2 (EHV-2), the herpesvirus saimiri (HVS) and found in the rhesus rhadinovirus (RRV) (Bertin et al., 1997; Hu et al., 1997; Searles et al., 1999; Thome et al., 1997). Two additional v-FLIP variants with carboxy-terminal extensions of unknown function are found in the human molluscipoxvirus (MCV) (Bertin et al., 1997; Hu et al., 1997; Thome et al., 1997).

Soon after the discovery of v-FLIP proteins, the mammalian cellular counterparts were identified, and called c-FLIP proteins (also called CASH, Casper, CLARP, FLAME, I-FLICE, MRIT or usurpin). Among 13 distinct c-FLIP splice variants which have been reported, only three are expressed as proteins: the 55 kDa long form (c-FLIPL), the 26 kDa short form (c-FLIPS) and the 24 kDa short form of c-FLIP (c-FLIPR), identified in the Raji B-cell line (Golks et al., 2005; Budd et al., 2006).



Genomic Organization and splice variants of c-FLAR (c-FLIP) gene. Schematic representation of the structure of the 48kb c-FLAR gene, which contains 14 exons and is transcribed into 11 alternative splice forms. The start and stop sites for translation of the various splice forms are indicated as arrowheads and asterisks, respectively. Only 3 proteins are expressed at the protein level: FLIPS, FLIPR and FLIPL (adapted from Djerbi M et al 2001).

Description

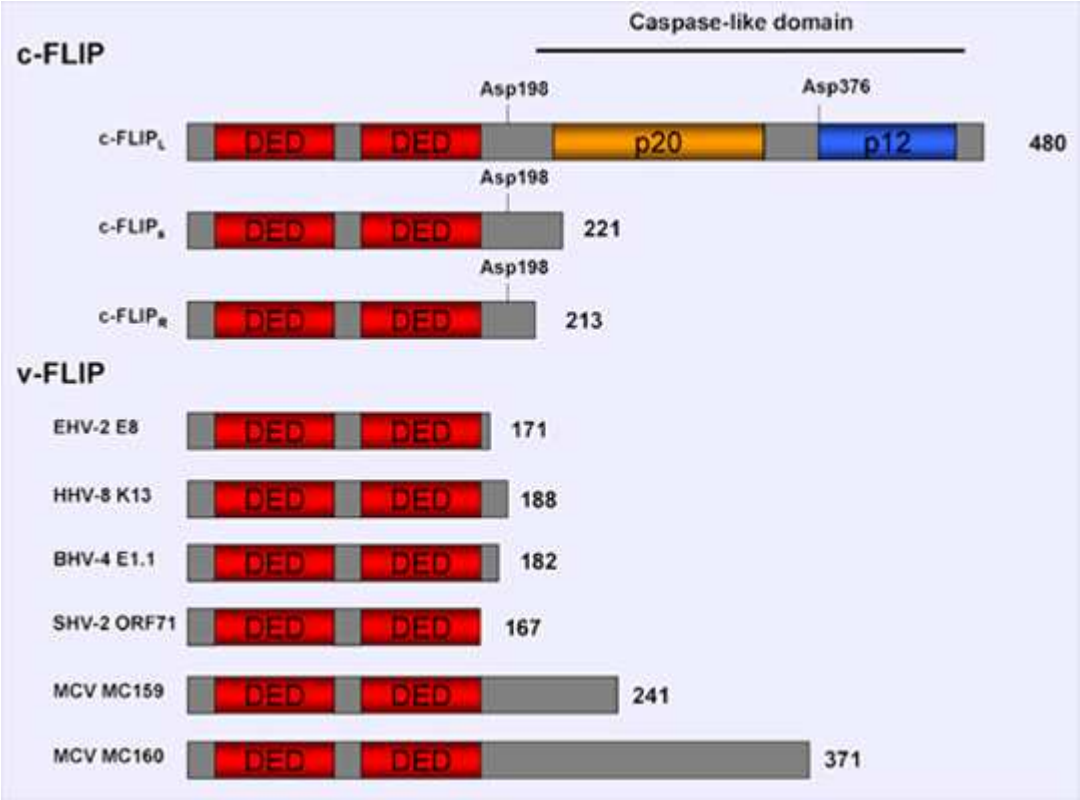
c-FLIPL is composed of 480 amino acids and contains a longer carboxy-terminus than cFLIPS. c-FLIPL closely resembles the overall structure of procaspase-8 and procaspase-10 (Figure 2). c-FLIPL contains two DEDs followed by a caspase-like domain. However, the C-terminal caspase-like domain of c-FLIPL lacks caspase enzymatic activity, owing to the substitution of several amino acids, including the crucial cysteine residue in the Gln-Ala-Cys-X-Gly motif (X: any amino acid) and the histidine residue in the His-Gly motif (Cohen, 1997). These two residues are necessary for caspase catalytic activity and are conserved in all caspases. c-FLIPL contains two conserved aspartic-acid cleavage sites: Asp-198, between DED2 and the p20-like domain; and Asp-376, between the p20- and p10-like domains, both of which can be cleaved during Fas- and TRAIL-induced apoptosis (Irmler, 1997; Scaffidi et al., 1999; Golks et al., 2006). This leads to the generation of p43-FLIP, which is implicated in the activation of different signalling pathways such as NF-kappa B pathway (Kataoka and Tschopp, 2004). In addition to NF-kappaB signaling, c-FLIPL has also been shown to activate Erk signaling pathway by binding to Raf-1 (Kataoka, 2000; Park et al., 2001).

The short form c-FLIPS is composed of 221 amino acids and has the same structure as vFLIP proteins, except that in addition to the two DEDs of cFLIPS, a carboxy-terminal tail composed of approximatively 20 amino acids is present that seems to be crucial for its ubiquitinylation and subsequent proteasomal degradation (Poukkula et al., 2005).

The short form c-FLIPR is composed of 213 amino acids, contains two DEDs and lacks the additional carboxy terminal amino acids present in c-FLIPS (Golks et al., 2005).

Expression

c-FLIPL is expressed in many tissues, most abundantly in the heart, skeletal muscle, lymphoid tissues and kidney. c-FLIP is abundantly and constitutively expressed in a wide array of normal cell types, including neurons, cardiac myocytes, endothelial cells, keratinocytes, pancreatic beta cells, dendritic cells (DCs), macrophages, CD34+ haematopoietic stem cells and spermatocytes (Ashany et al., 1999; Bouchet, 2002; Davidson et al., 2003; Desbarats, 2003; Giampietri, 2003; Kiener, 1997; Kim et al., 2002; Maedler, 2002; Marconi, 2004; Rescigno, 2000).



Overview of c-FLIP isoforms and v-FLIP isoforms. All the c-FLIP proteins carry two tandem death effector domains (DEDs). c-FLIPL also contains a caspase 8-like domain. The sites cleaved by procaspase-8 or by active caspase-8 are shown. Total number of amino acids is given.

c-FLIP is highly expressed in various types of tumour cells, including colorectal carcinoma (Ryu et al., 2001; Ullenhag et al., 2007), gastric carcinoma (Nam et al., 2003; Zhou et al., 2004), pancreatic carcinoma (Elnemr et al., 2001), Hodgkin's lymphoma (Dutton et al., 2004; Mathas et al., 2004; Thomas et al., 2002), B cell chronic lymphocytic leukemia (MacFarlane et al., 2002; Olsson et al., 2001), melanoma (Griffith et al., 1998), ovarian carcinoma (Abedini et al., 2004; Mezzanzanica et al., 2004), cervical carcinoma (Wang et al., 2007), bladder urothelial carcinoma and prostate carcinoma (Korkolopoulou et al., 2004; Zhang et al., 2004).

All of these tumours are often resistant to death receptor-mediated apoptosis. The expression of c-FLIP has been proven to be one of the major determinants of the resistance to death ligands such as FasL and TRAIL (TNF-related apoptosis-inducing ligand), and numerous reports have shown that down-regulation of c-FLIP results in sensitizing various resistant tumour cells to death ligands (Kim et al., 2000; Longley et al., 2006; Ricci et al., 2004; Wilson et al., 2007).

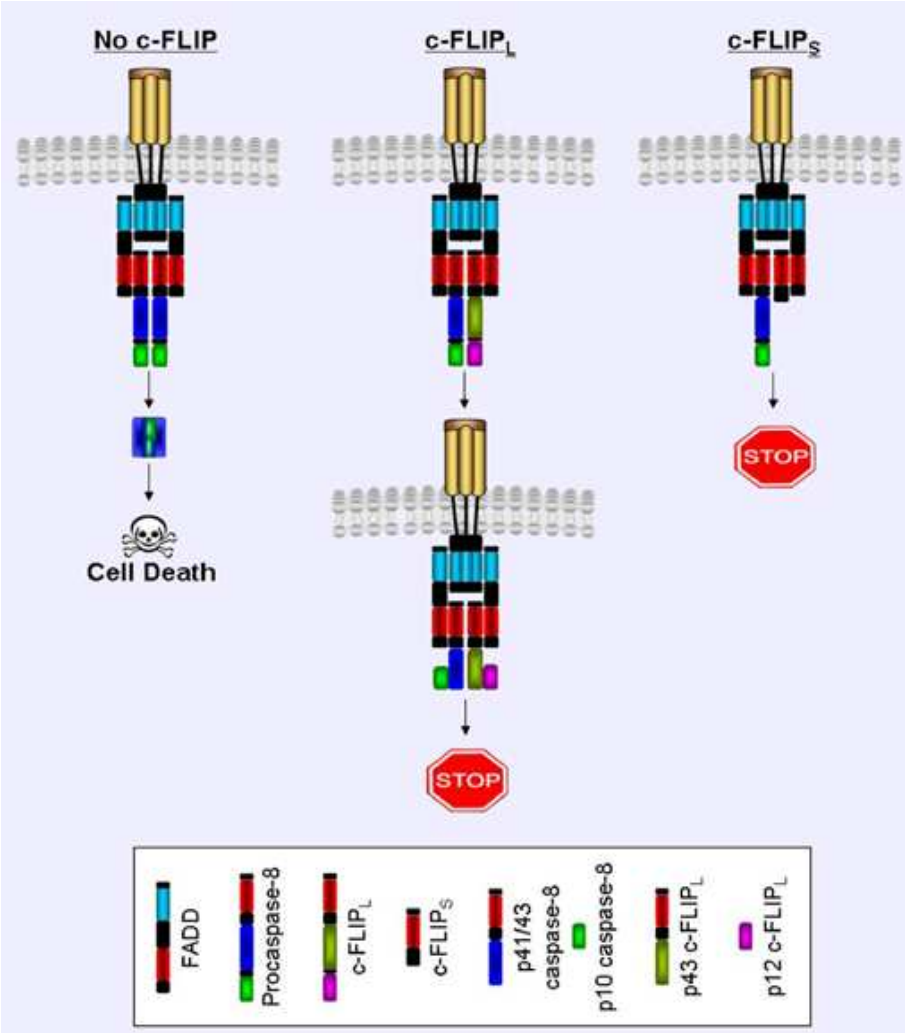
Localisation

c-FLIP proteins are localized in the cytosol.

Function

In many studies, in vitro, FLIP proteins (v-FLIP, c-FLIPR, c-FLIPS and c-FLIPL) protect cells against apoptosis induced by several death receptors, including FAS, tumour-necrosis factor (TNF) receptor 1 (TNFR1), TNF-related apoptosis-inducing ligand (TRAIL) receptor 1 (TRAILR1; also known as DR4), TRAILR2 (also known as DR5) and TNFR-related apoptosis-mediating protein (TRAMP; also known as DR3). Due to its high structural homology with procaspase-8, FLIP interferes with caspase-8 activation at the death-inducing signalling complex (DISC), which is formed after death receptor ligation (Ashkenazi and Dixit, 1999). The inhibition of Death Receptor-mediated apoptosis by FLIP is due to competition between the DEDs of FLIP and procaspase-8/10 for recruitment to the adaptor protein FADD at the DISC (Irmler, 1997; Srinivasula, 1997). Procaspase-8 recruitment to the DISC results in its homodimerization and two sequential cleavage steps that generate p10 and p18 fragments that heterodimerize to form fully active $(p10\text{-}p18)_2$ caspase-8 that dissociates from the DISC (Krammer et al., 2007).

When the death receptors are stimulated by their corresponding ligand, they recruit the adapter molecule FADD. FADD can then recruit DED containing proteins, e.g. caspase-8, and form a DISC. c-FLIP inhibits caspase-8 activation at the DISC. c-FLIPL and c-FLIPS have been shown to block death receptor-mediated apoptosis by forming a proteolytically inactive heterodimer with



Schematic diagram of c-FLIP recruitment to the DISC. All the c-FLIP proteins carry two tandem death effector domains (DEDs), which can bind FADD and procaspase-8. c-FLIPL is structurally very similar to procaspase-8 apart from the active site of c-FLIP in which cysteine 360 has been substituted by a tyrosine, and in another active site, histidine 317 has been substituted by an arginine in c-FLIPL.

procaspase-8 (Golks et al., 2005; Krueger et al., 2001). However, cleavage is blocked at different stages. For c-FLIPS and c-FLIPR, both cleavage steps required for procaspase-8 activation are completely blocked. In contrast, c-FLIPL allows partial cleavage of procaspase-8 at the DISC (Figure 3). When a molecule of procaspase-8 and c-FLIPL come into contact at the DISC, a conformational change in the two molecules occurs. This leads to the autocatalytic cleavage of the p10 subunit from procaspase-8. c-FLIPL is also partially cleaved by the procaspase-8 molecule to generate a p12 subunit. However, cleavage is stopped at this stage and no p18 subunit is generated from caspase-8. It has been hypothesised that the second reciprocal trans-catalytic cleavage step cannot occur because of the lack of the cysteine residue at the active site of c-FLIPL (Micheau, 2002). The resulting cleavage products are p41/43- and p10-caspase-8 products; and p43- and p12-c-FLIPL intermediates. Furthermore, Kreuger et al demonstrated that the p41/43-caspase-8 and p43-c-FLIPL intermediates remain bound at the DISC (Krueger et al., 2001). Recently, it has been proposed that the DISC-bound caspase 8/FLIP complex has catalytic activity that is not capable of generating a pro-apoptotic signal, but that can cleave local substrates such as RIP (receptor-interacting protein) (Micheau, 2002).

Implicated in

Hodgkin's lymphoma (cHD)

Note

Classical Hodgkin's lymphoma (cHL), a common human lymphoma, has been proposed to be derived from germinal centre (GC) B cells in the majority of cases (Kuppers et al., 2002). Among tumour-forming cells, the malignant Hodgkin/Reed-Sternberg (HRS) cells, which represents the malignant population of cHD disease, are rare and represent only 1% of cells in affected lymph nodes. HRS cells have lost their B cell phenotype, including immunoglobulin (Ig) expression

(Schwering et al., 2003). Usually, B cells with non-functional Ig expression undergo apoptosis.

Disease

Hodgkin/Reed-Sternberg (HRS) cells are most often resistant to Death receptor-mediated apoptosis such as is mediated by FasL or TRAIL. The expression of c-FLIP has been proven to be one of the major determinants of this resistance. HRS cells have been shown to overexpress c-FLIP proteins in a NF-kappa B-dependent manner. Some studies have shown that the high level of c-FLIP prevent the activation of caspase-8 by inhibition of procaspase-8 processing. To remove this resistance to Death receptor mediated apoptosis, some reports have shown that specific down-regulation of c-FLIP by small interfering RNA oligoribonucleotides strategies is sufficient to sensitize HRS cells to Fas and TRAIL-induced apoptosis (Mathas et al., 2004).

Colorectal cancer (CRC)

Note

Colorectal cancer is a major cause of cancer mortality. Response rates in the advanced disease setting are of the order of 45% to 50% for the most effective drug combinations. Drug resistance is a major problem in this disease (and other cancers) and is often the result of insufficient apoptosis induced by chemotherapy.

Disease

Clinical studies have demonstrated significantly elevated c-FLIP expression in colorectal tumours (Ryu et al., 2001), suggesting that c-FLIP may be play a role in the pathogenesis of this disease. Indeed, c-FLIP(L) overexpression was associated with poor prognosis in colorectal cancer patients (Ullenhag et al., 2007).

Graves' disease

Note

Graves' disease is an autoimmune form of hyperthyroidism. In the context of this disease, lymphocyte TH2 cells infiltrate the thyroid gland and, via production of IL4 and IL10, stimulate thyrocytes to become more resistant to Fas-mediated apoptosis, in part by upregulation of c-FLIP and Bcl-XL (Stassi, 2000).

Multiple sclerosis (MS)

Note

Multiple sclerosis (MS): a neuroinflammatory disease that is thought to have an autoimmune basis due to autoreactive T cells responding to myelin self-antigens (Conlon et al., 1999). Autoimmune diseases such as MS can result from the lack of elimination of pathogenic, autoreactive lymphocytes.

Disease

In this disease, the pathological upregulation of FLIP levels in T cells might contribute to the accumulation of lymphocytes in cortical-spinal-fluid and accumulation of activated-peripheral T cells in patients with clinically active MS. FLIPL and FLIPS were found to be specifically overexpressed in T cells of MS patients, indicating that abnormally high FLIP expression levels might extend the viability of potentially pathogenic, autoreactive T cells in the context of this disease (Semra et al., 2001; Sharief, 2000).

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