Gene Section
Review

CASP8 (Caspase 8, Apoptosis-Related Cysteine Peptidase)

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Abstract
Review on CASP8, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity
Other names: ALPS2B, CAP4, Casp-8, FLICE, MACH, MCH5
HGNC (Hugo): CASP8
Location: 2q33.1
Local order: CASP8 is located on chromosome 2 on the long arm (positive strand), and lies between the CASP10 and STRADB genes.

DNA/RNA
Description
54269 bases with 11 exons.

Transcription
There are 6 transcriptional variants of CASP8 and they are described in Table 1.

Protein
Note
Caspases are a family of cysteinyl aspartate specific proteases which are synthesized as zymogens. Caspase-8 was discovered as a component of the CD95 (Fas/APO-1) death-inducing signaling complex (DISC) (Muzio et al., 1996).

Description
Caspase-8 has a number of isoforms, including procaspase-8a (496 aa), procaspase-8b (479 aa), procaspase-8c (464 aa), procaspase-8e (235 aa), procaspase-8g or caspase-8L (538 aa) and caspase-8 short (108 aa). Only two isoforms are predominantly expressed in many different tissues and cell lines: procaspase-8a and procaspase-8b (Scaffidi et al., 1997). They act as the main initiator caspases in death receptor-induced apoptosis.

Table 1

<table>
<thead>
<tr>
<th>Transcript</th>
<th>Accession no.</th>
<th>Exon number</th>
<th>Sequence length</th>
<th>Coding sequence length</th>
<th>Encoding protein</th>
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<td>1491</td>
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<tr>
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<td>1440</td>
<td>procaspase-8b</td>
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<tr>
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<td>8</td>
<td>2665</td>
<td>1395</td>
<td>procaspase-8c</td>
</tr>
<tr>
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<td>8</td>
<td>1123</td>
<td>708</td>
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</tr>
<tr>
<td>F</td>
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<td>2750</td>
<td>1395</td>
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</tr>
<tr>
<td>G</td>
<td>NM_001080125.1</td>
<td>9</td>
<td>2938</td>
<td>1617</td>
<td>procaspase-8L</td>
</tr>
</tbody>
</table>
Caspase-8L was reported to be expressed in human peripheral blood lymphocytes as a truncated protein, which lacks the C-terminal protease domain (Horiiuchi et al., 2000). Therefore, it is suggested that caspase-8L is recruited into the DISC but remains proteolytically inert, interfering with the transduction of the signal from the DISC (Himeji et al., 2002). An isoform that is detected in bone marrow mononuclear cells is named caspase-8 short. Although it only contains the first DED and a part of the second DED, overexpression of caspase-8 short is reported to increase sensitivity to apoptosis (Xu et al., 2009).

In addition to caspase-8 isoforms, there is a number of cleavage products described, which are formed in the course of apoptosis. Apoptotic processing of procaspase-8a/b involves generation of the cleavage products p43/p41, p30, the prodromes p26/p24, p18 and p10 (Hoffmann et al., 2009). The latter two cleavage products form the active caspase-8 heterotetramer p10−p18, that triggers apoptosis (Lavrik and Krammer, 2012).

Expression

Caspase-8 is expressed in almost all kind of tissues, with the highest expression in the immune system and lowest in the nervous system (McCall et al., 2011).

Localisation

Procaspase-8 mainly localizes to the cytosol, in close proximity to the membrane (Medema et al., 1997). It may also localize to mitochondria (Qin et al., 2001; Chandra et al., 2004) or centrosomes (Mielgo et al., 2009). Caspase-8 cleavage products are reported to localize to the nucleus as well as the cytosol (Benchoua et al., 2002; Yao et al., 2007).

Function

Caspase-8 is the main initiator caspase in death receptor-induced apoptosis. Upon stimulation, procaspase-8 is recruited to the CD95 or TRAIL DISC, or TNF complex II. Procaspase-8 activation involves dimerization, oligomerization and cleavage (Schleich et al., 2012). The cleavage of procaspase-8 involves several steps, leading to the generation of the active caspase-8 heterotetramer p10−p18, that triggers apoptosis (Lavrik and Krammer, 2012). Depending on the cell type, active caspase-8 either directly cleaves effector caspases (caspase-3 and caspase-7) or cleaves Bid, which eventually leads to release of cytochrome C and apoptosome formation followed by cleavage of effector caspase-3, caspase-6 and caspase-7 by procaspase-9 (Scaffidi et al., 1998; Scaffidi et al., 1999).

In addition to apoptosis, caspase-8 has a role in programmed necrosis (necroptosis) as well. Caspase-8 can be recruited to the necroptotic complexes (necrosome or ripoptosome) together with RIP1, RIP3 and FADD.
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Schematic representation of the structure of the 54 kb CASP8 gene, which contains 10 exons and can be transcribed into 6 alternative splice variants.

Interestingly, although the activation of procaspase-8 to p10α-p18β heterotetramer is necessary for MAPK signaling (Kober et al., 2011), it is not necessary for NF-kB signaling upon CD95 stimulation (Neumann et al., 2010).

Caspase-8 has been also reported to affect metastasis. Interestingly, although loss of caspase-8 potentiates metastasis, under conditions where apoptosis is compromised, caspase-8 can promote tumor cell migration and metastasis (Stupack et al., 2006; Barbero et al., 2009).

**Homology**
Caspase-10, FADD, c-FLIP.

**Mutations**

**Germinal**
A homozygous C to T mutation at residue 248 leads to familial autoimmune lymphoproliferative syndrome type 2B.

**Somatic**
Various somatic mutations of CASP8 are identified in different carcinomas. Mutations are observed at different parts of caspase-8, but they all lead to a catalytically inactive form.

- Hepatocellular carcinoma: CASP8 is frequently inactivated by the frameshift somatic mutation 1225-1226delTG in hepatocellular carcinomas, resulting in a premature termination of amino-acid synthesis in the p10 protease subunit (Soung et al., 2005b).
- Gastric carcinoma: Inactivating CASP8 mutations are detected at different sites in about 10% of advanced gastric carcinomas (Soung et al., 2005a).
- Colorectal carcinoma: Inactivating CASP8 mutations are detected at different sites in about 5% of invasive colorectal carcinomas (Kim et al., 2003).
- Vulvar squamous carcinoma: Deletion of leucine 62 (ΔLeu62casp-8) is detected in A431 human vulvar squamous carcinoma cells. ΔLeu62casp-8 has a shorter half-life than wild-type caspase-8 and cannot interact with caspase-8 or FADD; therefore lost its proapoptotic activity (Liu et al., 2002).
- Head and neck carcinoma: A mutation was detected in the tumor cells from head and neck carcinoma that modifies the stop codon and lengthening the protein by 88 amino acids (Mandruzzato et al., 1997).
- Neuroblastoma: An Alanine to Valine missense mutation was detected at codon 96 in a neuroblastoma sample which lacks CASP8 mRNA expression (Takita et al., 2001).

**Implicated in**

**Hepatocellular carcinoma**
**Disease**
Hepatocellular carcinoma accounts for the majority of liver cancers. Mostly, it is secondary to cirrhosis, which is caused mainly by alcohol abuse or hepatitis B/C infections. A somatic mutation in CASP8 leading to deletion of the bases 1225-1226 was detected in 9 out of 69 hepatocellular carcinoma samples from unrelated patients. This deletion results in a frameshift and therefore premature termination of amino-acid synthesis in the p10 protease subunit, consequently inactivating caspase-8 (Soung et al., 2005b).

**Gastric carcinoma**
**Disease**
Gastric carcinomas arise from the epithelium of the stomach. In a study by Soung and colleagues (Soung et al., 2005a), 122 advanced gastric carcinoma samples were analyzed for mutations in the coding region and the exon-intron junctions of CASP8 gene by PCR-SSCP analysis. In 13 samples, mutations in caspase-8 were found. All mutants were still expressed at a similar level compared to wild-type caspase-8, however, when transfected into cell lines, all mutants except one showed defects in apoptosis.
**Involvement of procaspase-8 in death-receptor signaling.** (A) Procaspase-8 is recruited to the CD95 or TRAIL DISC through the adaptor protein FADD. Upon activation of TNF, procaspase-8 is recruited through FADD and TRADD. For activation, procaspase-8 requires dimerization and internal cleavage. The major function of procaspase-8 in DR signaling is induction of apoptosis, but it also regulates necroptosis or NF-κB via RIP1/RIP3 and c-FLIP(L). (B) Procaspase-8 consists of a prodomain harboring tandem death effector domains (DED) followed by one large (p18) and one small (p10) catalytic subunit. Cleavage between p18 and p10 generates the intermediate p43/p41 which is further processed to the fully active form by cleavage between the prodomain and p18.

**Colorectal carcinoma**

**Disease**
Colorectal cancer arises from colon, rectum or appendix. In the analysis of 82 colorectal adenomas and 98 invasive colorectal carcinomas, 5 mutations were detected only in the colorectal carcinomas but not in the adenomas. 3 out of 5 of these mutations acted in a dominant negative manner and suppressed apoptosis (Kim et al., 2003).

**Vulvar squamous carcinoma**

**Disease**
In the analysis of A431 human vulvar squamous carcinoma cells, a mutation in CASP8 leading to deletion of leucine 62 was detected. This mutant version of caspase-8 retained its enzymatic activity, however, it lost the ability to interact with itself, wild-type caspase-8 or FADD and therefore lost its proapoptotic activity (Liu et al., 2002).

**Head and neck carcinoma**

**Disease**
Head and neck carcinomas start in the lip, oral cavity, nasal cavity, paranasal sinuses, pharynx, or larynx and the majority (90%) originates from the epithelium, therefore named squamous cell carcinomas. A mutation in CASP8 was detected in the cells from a tumor relapse resected from the oral cavity of a late-stage squamous cell carcinoma patient. This mutation was found to modify the stop codon and add an Alu repeat to the coding region. Therefore, the mutant protein is 88 amino acids longer than the wild type and cannot efficiently act as an apoptotic protein (Mandruzzato et al., 1997).

**Neuroblastoma**

**Disease**
Neuroblastoma arises from immature nerve cells. It is mainly localized to adrenal medulla. In a study
where human neuroblastoma cells were transferred to chick chorioallantoic membrane, tumor development was monitored. Although presence or lack of caspase-8 did not change primary tumor growth, metastasis was highly promoted in the tumors lacking caspase-8 due to impaired programmed cell death (Stupack et al., 2006).

In a similar study, tumor cells additionally lacking caspase-3 were used to test non-apoptotic effects of caspase-8 on neuroblastoma metastasis. Interestingly, tumors lacking only caspase-3 metastasized more efficiently than tumors lacking both caspas, pointing out that caspase-8 also shows non-apoptotic properties such as enhancing cell migration (Barbero et al., 2009).

Silencing of caspase-8 was also observed in human neuroblastoma samples. In two studies by Takita and colleagues, 11 out of 15 and 19 out of 27 neuroblastoma samples did not express caspase-8, detected by real-time PCR (Takita et al., 2000; Takita et al., 2001).

Furthermore, a missense mutation was detected at codon 96 in one of the samples lacking caspase-8 expression (Takita et al., 2000). Furthermore, silencing of CASP8 in neuroblastoma was found to be associated with MYCN amplification. 10 out of 16 patients with MYCN amplification had completely methylated CASP8 alleles opposed to only 1 out of 26 patients without MYCN amplification. Interestingly, one patient among these 42 patients had a deletion of the CASP8 gene (Teitz et al., 2000).

**Medulloblastoma**

**Disease**
Medulloblastoma is a tumor of the brain that originates in the cerebellum or posterior fossa. In one study of medulloblastoma, 14 out of 27 tumors were identified to have lost CASP8 mRNA expression (Zuzak et al., 2002). Furthermore, another study showed that CASP8 expression was reversely correlating with the disease. The 5-year cumulative progression-free survival rate of the patients with weak CASP8 expression was 31%, and with moderate/strong caspase-8 expression 73% (Pingoud-Meier et al., 2003).

**Small cell lung carcinoma**

**Disease**
Small cell lung carcinomas commonly originate from the lung, although rarely can originate also from cervix, prostate or gastrointestinal tract. In this carcinoma, tumor cells are much smaller than normal cells with almost no cytoplasm. In one study, 13 out of 25 small cell lung carcinoma samples showed silencing of CASP8 due to methylation (Hopkins-Donaldson et al., 2003).


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