CASP1 (caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase))
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Identity
Hugo: CASP1
Other names: ICE; IL1BC; P45
Location: 11q22.3
Local order: ICEBERG, INCA1, INCA2, COP, Caspase-1, Caspase-5, Caspase-4.

The human caspase-1 cluster contains caspase-1 and four other genes encoding decoy caspases: cop, inca1, inca2 and iceberg. These decoy caspases are absent in the mouse genome, suggesting their occurrence recently by duplication of caspase-1 during evolution.

Note: 11q22.2-q22.3: a site frequently involved in rearrangement in human cancers.
**DNA/RNA**

**Description**

The human caspase-1 gene is comprised of 10 exons, spanning 10.6 kb on chromosome 11q22.2-q22.3.

**Transcription**

Six alternatively spliced forms of caspase-1 have been identified in Homo sapiens. The longest termed CASP1alpha is 1364 bp with an ORF encoding 404 amino acids (aa) and is the most predominant isoform. CASP1beta is 1185 bp, lacks entire exon3 (275-338 bp; 92-112 aa), ORF encoding 383 aa. CASP1gamma is 969 bp, lacks most of exon2 and entire exon3 (59-338 bp; 20-112 aa), ORF encoding 291 aa. CASP1delta is 825 bp, lacks entire exon7 (863-1006 bp; 288-335 aa), ORF encoding 356 aa. CASP1epsilon is 300 bp, lacks most of exon2 and exon3-exon7 (59-1006 bp; 20-335 aa), ORF encoding 98 aa. CASP1zeta is 1131 bp, missing 79 bp in prodomain of caspase-1, ORF encoding 365 aa. Among these alpha, beta, gamma and zeta forms are proteolytically active and can induce apoptosis. As delta and epsilon lack part of the catalytic domain, they do not induce apoptosis and serve as inhibitors of caspase-1 when overexpressed.

**Pseudogene**

COP (Card Only Protein).
**Protein**

**Description**

Caspase-1 is the prototypical member of a subclass of caspases involved in cytokine maturation termed inflammatory caspases that also include caspases-4, caspases-5, and caspases-12. It is also involved in some forms of apoptosis. Caspase-1 protein consists of an N-terminal CARD (caspase activation and recruitment domain), a large P20 subunit and a small P10 subunit. Due to its long N-terminal prodomain, caspase-1 belongs to the initiator group of caspases and is therefore suspected to act proximally in a caspase activation cascade leading to apoptosis.

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**Table 1: List of known caspase-1 substrates**

<table>
<thead>
<tr>
<th>Substrates of Caspase-1</th>
<th>Cleavage Site</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β</td>
<td>YVAD27/I116</td>
<td>Essential Inflammatory Mediator/Innate Immunity</td>
</tr>
<tr>
<td>IL-18</td>
<td>LESD36</td>
<td>Stimulates IFN-γ production</td>
</tr>
<tr>
<td>IL-33</td>
<td>ALHD110</td>
<td>Induces expression of IL-4, IL-5 and IL-13</td>
</tr>
<tr>
<td>ICAD</td>
<td>DETD117</td>
<td>Induces DNA Fragmentation</td>
</tr>
<tr>
<td>Parkin</td>
<td>LHDT126</td>
<td>Triggers Dopaminergic Cell death</td>
</tr>
<tr>
<td>CrmA</td>
<td>LVAD303</td>
<td>Caspase Inhibitory Action</td>
</tr>
<tr>
<td>Huntingtin</td>
<td>Not known</td>
<td>Aggregation</td>
</tr>
<tr>
<td>Phospholipase A2</td>
<td>YQSD459</td>
<td>Inactivates the proinflammatory enzymes</td>
</tr>
<tr>
<td>Caspase-6</td>
<td>Not Known</td>
<td>Induces Caspase-6 mediated Neuronal cell death</td>
</tr>
<tr>
<td>Mal (MyD88 adaptor like)</td>
<td>YYVD198</td>
<td>Regulation of TLR2 and TLR4 signalling pathway</td>
</tr>
<tr>
<td>Actin</td>
<td>LVVD111/ELPD244</td>
<td>Activation of DNase I and Depolymerization of Actin</td>
</tr>
<tr>
<td>p63</td>
<td>YYED185</td>
<td>Cell proliferation during Oncogenesis</td>
</tr>
</tbody>
</table>

**Table 2: List of Caspase-1 interacting proteins**

<table>
<thead>
<tr>
<th>Interacting Proteins for Caspase-1</th>
<th>Activating /Inhibitory Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICEBERG</td>
<td>Inhibitor</td>
</tr>
<tr>
<td>RIP2</td>
<td>Activator</td>
</tr>
<tr>
<td>NLRC4</td>
<td>Activator</td>
</tr>
<tr>
<td>ASC</td>
<td>Activator</td>
</tr>
<tr>
<td>COP</td>
<td>Inhibitor</td>
</tr>
<tr>
<td>PYNOD</td>
<td>Inhibitor</td>
</tr>
<tr>
<td>INCA 1 &amp; 2</td>
<td>Inhibitor</td>
</tr>
<tr>
<td>PYPAF</td>
<td>Activator</td>
</tr>
<tr>
<td>Pyrin</td>
<td>Activator</td>
</tr>
<tr>
<td>NOD1</td>
<td>Activator</td>
</tr>
<tr>
<td>CARD8/CARDINAL</td>
<td>Inhibitor</td>
</tr>
<tr>
<td>SipB</td>
<td>Activator</td>
</tr>
<tr>
<td>Ipaf</td>
<td>Activator</td>
</tr>
<tr>
<td>Serp2</td>
<td>Inhibitor</td>
</tr>
<tr>
<td>CrmA</td>
<td>Inhibitor</td>
</tr>
</tbody>
</table>
Caspase-1 is synthesized as a proenzyme of 45 kDa, which undergoes proteolytic cleavage at Asp residues to produce the active enzyme. The active caspase-1 enzyme is a heterotetramer comprised of two P20 and two P10 subunits. The catalytic site is formed by amino acids from both P20 and P10 subunits, with the active cysteine located within the P20 subunit. Caspase-1 is activated through interactions with other CARD containing proteins such as ASC, RIP2 and NLRC4 via homotypic CARD-CARD interactions. Bacterial and viral proteins like SipB, IpaB, CrmA, and Serp2 which do not contain the CARD domain, also regulate caspase-1. Caspase-1 is activated by phosphorylation at serine 376 residue by PAK1 upon Helicobacter pylori infection.

Expression
Caspase-1 is highly expressed in leukocytes, monocytes and epithelial cells. Caspase-1 gene expression is induced in response to various stimuli such as microbial infections (Mycobacterium avium, Salmonella typhimurium, Legionella pneumophila, Bacillus anthracis, Francisella tularensis and bacterial LPS), cytokines (IFN-gamma and TNF-alpha), and DNA damaging agents (Doxorubicin, UV radiation and Paclitaxel). Levels of caspase-1 mRNA are high in ischemic tissues. Tumor suppressor p53, p73, SP1, ETS-1, IFT57/HIPPI and IRF-1 activate transcription of full length caspase-1 mRNA by binding to respective sites in the promoter, within a region 550 bp upstream of the transcription start site.

Localization
Predominantly cytoplasmic. See Table-1 and Table-2.

Function
The adaptor molecules ASC, NLRC4 and Cryopyrin/Nalp3 regulate caspase-1 within a multiprotein complex known as the 'Inflammasome'. Caspase-1 activation results in cleavage and activation of proinflammatory cytokines such as IL-1beta and IL-18. Caspase-1 deficient mice have a defect in the maturation of proIL-1beta and are resistant to the lethal effect of endotoxins. Various pathogens such as S. typhimurium (TypeIII secretion), L. pneumophila (Type IV secretion), B. anthracis (Lethal Toxin), F. tularensis activate caspase-1 through 'inflammasomes'. Caspase-1 activation also occurs upon exposure to bacterial RNA, imidazoquinoline compounds, LPS, extracellular ATP, muramyl dipeptide (MDP), monosodium urate, calcium pyrophosphate dehydrate and other TLR ligands via 'inflammasomes'. In addition to bacterial pathogens, viral infection also induces caspase-1 activation. Caspase-1 acts apically in neuronal cell death pathways induced by hypoxia and ischaemia. Caspase-1 is also involved in p53-mediated apoptosis in a cell type specific manner. Caspase-1 sensitizes cells to death induced by agents like Fas ligand, radiation and cisplatin. Caspase-1 stimulates membrane biogenesis to repair damage caused by pore-forming toxins, thereby promoting host cell survival.

Homology
CARD of caspase-1 bears significant homology with the CARDs of Caspase-4, Caspase-5, SFRS2IP/Caspase-11, Caspase-12, ICEBERG, Nod1, NLRC4, NEDD2, cIAP2, cIAP3 and ced3.

Mutations
Germlinal
Not known.
Somatic
Not known.

Implicated in
Various diseases
Disease
In diseases such as ischemic and hypoxia induced brain injury, acute bacterial meningitis, ischemia of the heart and kidney. A role for caspase-1 has been implicated in Amyotrophic Lateral Sclerosis, Huntington’s disease, Parkinson’s disease, Crohn’s disease, Age-related cognitive dysfunctions, spinalcord inflammation and gout. Caspase-1 activation is enhanced in patients with CINCA syndrome.

Cancers
Disease
In ovarian cancer and stomach cancer: there is a decreased expression of caspase-1.

References


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This article should be referenced as such: