Caspase-6 3.4.22.59

1 Nomenclature

EC number
3.4.22.59

Recommended name
caspase-6

Synonyms
C14.005 (Merops-ID)
Csp-6 <3> [21]
MCH2
apoptotic protease Mch-2
caspase 6 <3, 4> [22, 24, 26, 28]

CAS registry number
182372-15-2

2 Source Organism

<1> *Gallus gallus* (no sequence specified) [23]
<2> *Mus musculus* (no sequence specified) [8, 25]
<3> *Homo sapiens* (no sequence specified) [4, 5, 6, 7, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 29, 30, 31]
<4> *Rattus norvegicus* (no sequence specified) [25, 28]
<5> *Xenopus laevis* (no sequence specified) [3]
<6> *Homo sapiens* (UNIPROT accession number: P55212) [1,2,9]
<7> *Mus musculus* (UNIPROT accession number: O08738) [10]

3 Reaction and Specificity

Catalyzed reaction
strict requirement for Asp at position P1 and has a preferred cleavage sequence of Val-Glu-His-Asp-/-

Reaction type
hydrolysis of peptide bond

Natural substrates and products

S SATB1 + H_2O <3> (<3> cleavage disrupts PDZ domain-mediated dimerization, causing detachment from chromatin early in T-cell apoptosis [13]) (Reversibility: ?) [13]
P ?
S Ufd2p + H_2O <3> (<3> cleavage of polyubiquitination factor Ufd2p at Asp123 within the putative regulatory N-terminal domain might have important functional consequences within the apoptotic cascade [14]) (Reversibility: ?) [14]
P ?
S β-catenin + H_2O <2> (<2> processing of β-catenin, production of a 70000 Da fragment [8]) (Reversibility: ?) [8]
P ?
S lamin A + H_2O <3> (<3> cleavage site is VEID-/- [7]) (Reversibility: ?) [7]
P ?
S poly(ADP-ribose)polymerase + H_2O <6> (<6> the enzyme may participate in poly(ADP-ribose)polymerase cleavage observed during apoptosis [9]) (Reversibility: ?) [9]
P ?
S pro-caspase-6 + H_2O <3> (<3> caspase-8 activates caspase-3, and caspase-3 in turn activates caspase-6. Caspase 3 has a major role in nuclear apoptosis [20]) (Reversibility: ?) [20]
P ?
S pro-caspase-8 + H_2O <3> (<3> caspase-6 is the major activator of caspase-8 in the cytochrome c-induced apoptosis pathway. Caspase-8 precursor is initially cleaved between the p18 and p10 domains resulting in fragments of 42000 Da and 10000 Da. The 42000 Da fragment is further cleaved resulting in fragments of 25000 Da and 18000 Da [11]) (Reversibility: ?) [11]
P ?
S transcription factor AP-2α + H_2O <3> (<3> AP-2α is cleaved is at Asp19 of the sequence DRHD19 by casoase-6 before DNA framentation during TNF-α-induced apoptosis [15]; <3> activates caspase-6 which in turn cleaves transcription factor AP2α [16]) (Reversibility: ?) [15, 16]
P ?
S viral nucleocapsid protein of transmissible gastroenteritis coronovirus + H_2O <3> (<3> cleavage site VVPD359-/-. Destruction of viral protein by the host cell death machinery [12]) (Reversibility: ?) [12]
P ?
S Additional information <3, 7> (<7> overexpression induces apoptosis [10]; <3> the enzyme has a major role in nuclear apoptosis [20]) (Reversibility: ?) [10, 2]
P ?

Substrates and products

- **S** Ac-VEID-7-amido-4-methylcoumarin + H_2O <4> (Reversibility: ?) [28]
- **P** Ac-VEID + 7-amino-4-methylcoumarin
- **S** DEVD-7-amido-4-methylcoumarin + H_2O <6> (Reversibility: ?) [9]
- **P** DEVD + 7-amido-4-methylcoumarin
- **S** IETD-7-amido-4-trifluoromethylcoumarin + H_2O <2, 3, 4> (<4> very low cleavage activity [25]) (Reversibility: ?) [25]
- **P** IETD + 7-amino-4-trifluoromethylcoumarin
- **S** SATB1 + H_2O <3> (<3> specifically cleaves at amino acid position 254 to produce a 65000 Da major fragment containing both a base-unpairing region (BUR)-binding domain and a homeodomain. This cleavage separates the DNA-binding domains from amino acids 90 to 204, a region which is a dimerization domain. The resulting SATB1 monomer loses its BUR-binding activity [13]; <3> cleavage disrupts PDZ domain-mediated dimerization, causing detachment from chromatin early in T-cell apoptosis [13]) (Reversibility: ?) [13]
- **P** ?
- **S** Tau + H_2O <3> (<3> cleavage of the microtubule-stabilizing protein by Csp-6 [21]; <3> microtubule-associated protein, caspase-6 cleaves the N-terminus at D13 of tau in vitro [27]) (Reversibility: ?) [21, 27]
- **P** ?
- **S** Ufd2p + H_2O <3> (<3> polyubiquitination factor Ufd2p is cleaved at Asp123 [14]; <3> clavage of polyubiquitination factor Ufd2p at Asp123 within the putative regulatory N-terminal domain might have important functional consequences within the apoptotic cascade [14]) (Reversibility: ?) [14]
- **P** ?
- **S** VEID-7-amido-4-trifluoromethylcoumarin + H_2O <3> (Reversibility: ?) [31]
- **P** VEID + 7-amido-4-trifluoromethylcoumarin
- **S** VEID-7-amido-4-trifluoromethylcoumarin + H_2O <2, 3, 4> (<2,3> preferred substrate for caspase-6 [25]) (Reversibility: ?) [25]
- **P** VEID + 7-amino-4-trifluoromethylcoumarin
- **S** acetyl-DEVD-4-nitroanilide + H_2O <3> (Reversibility: ?) [18]
- **P** acetyl-DEVD + 4-nitroaniline
- **S** acetyl-DQMD-4-nitroanilide + H_2O <3> (Reversibility: ?) [18]
- **P** acetyl-DQMD + 4-nitroaniline
- **S** acetyl-VDQQD-4-nitroanilide + H_2O <3> (Reversibility: ?) [18]
- **P** acetyl-VDQQD + 4-nitroaniline
- **S** acetyl-VEHD-7-amido-4-methylcoumarin + H_2O <3> (<3> VEHD is the optimal tetrapeptide recognition motif [5]) (Reversibility: ?) [5]
- **P** acetyl-VEHD + 7-amino-4-methylcoumarin
- **S** acetyl-VEID-4-nitroanilide + H_2O <3> (Reversibility: ?) [18]
- **P** acetyl-VEID + 4-nitroaniline
- **S** acetyl-VQVD-4-nitroanilide + H_2O <3> (Reversibility: ?) [18]
- **P** acetyl-VQVD + 4-nitroaniline
- **S** acetyl-YEVD-4-nitroanilide + H_2O <3> (Reversibility: ?) [18]

P acetyl-YEVD + 4-nitroaniline
S β-catenin + H_2O <2> (<2> processing of β-catenin, production of a 70000 Da fragment [8]) (Reversibility: ?) [8]
P ?
S cFLIP + H_2O <3> (Reversibility: ?) [29]
P ?
S lamin A + H_2O <3> (<3> apoptotic cleavage [23]) (Reversibility: ?) [23]
P ?
S lamin A + H_2O <3> (<3> cleavage site is VEID-/- [7]) (Reversibility: ?) [7, 30, 31]
P ?
S nuclear mitotic apparatus protein + H_2O <3> (<3> cleavage at sites distict from caspase-3 [20]) (Reversibility: ?) [20]
P ?
S *p*-nitroanilide-labeled substrate + H_2O <3> (Reversibility: ?) [24]
P ?
S periplakin + H_2O <3> (<3> caspase 6 cleaves periplakin at an unconventional recognition site, amino acid sequence TVAD [26]) (Reversibility: ?) [26]
P ?
S poly(ADP-ribose)polymerase + H_2O <6> (<6> the enzyme may participate in poly(ADP-ribose)polymerase cleavage observed during apoptosis [9]) (Reversibility: ?) [9]
P ?
S pro-caspase-6 + H_2O <3> (<3> caspase-8 activates caspase-3, and caspase-3 in turn activates caspase-6. Caspase 3 has a major role in nuclear apoptosis [20]) (Reversibility: ?) [20]
P ?
S pro-caspase-8 + H_2O <3> (<3> caspase-8 precursor is initially cleaved between the p18 and p10 domains resulting in fragments of 42000 Da and 10000 Da. The 42000 Da fragment is further cleaved resulting in fragments of 25000 Da and 18000 Da [11]; <3> caspase-6 is the major activator of caspase-8 in the cytochrome c-induced apoptosis pathway. Caspase-8 precursor is initially cleaved between the p18 and p10 domains resulting in fragments of 42000 Da and 10000 Da. The 42000 Da fragment is further cleaved resulting in fragments of 25000 Da and 18000 Da [11]) (Reversibility: ?) [11]
P ?
S topoisomerase I + H_2O <3> (<3> cleavage at PEDD123-/-G and EEED170-/-G [19]) (Reversibility: ?) [19]
P ?
S transcription factor AP-2α + H_2O <3> (<3> cleaves at Asp19 of the sequence DRHD19 [15]; <3> AP-2α is cleaved is at Asp19 of the sequence DRHD19 by casoase-6 before DNA framentation during TNF-α-induced apoptosis [15]; <3> activates caspase-6 which in turn cleaves transcription factor AP2α [16]) (Reversibility: ?) [15, 16]
P ?

S viral nucleocapsid protein of transmissible gastroenteritis coronovirus + H_2O <3> (<3> cleavage site VVPD359-/- [12]; <3> cleavage site VVPD359-/-. Destruction of viral protein by the host cell death machinery [12]) (Reversibility: ?) [12]
P ?
S Additional information <3, 6, 7> (<6> Mch2α but not Mch2β possesses protease activity [9]; <3> the preferred cleavage sequence is VEHD-/- [6,7]; <7> overexpression induces apoptosis [10]; <3> the enzyme has a major role in nuclear apoptosis [20]) (Reversibility: ?) [6, 7, 9, 10, 20]
P ?

Inhibitors

4-hydroxy-5-iodo-3-nitrophenylacetyl-Leu-Leu-Leu-vinylsulfone <3> [25]
DMSO <3> [30]
IETD-CHO <2> (<2> caspase-6 in lens extracts from neonatal mice partially inhibited by 0.0005 mM [25]) [25]
VEID-CHO <2> (<2> caspase-6 in lens extracts from neonatal mice efficiently inhibited by 0.0005 mM [25]) [25]
VEID-FMK <3> [30]
Z-VEID-fmk <3> [31]
Z-Val-Ala-ASp-fluoromethylketone <3> (<3> inhibitor of caspases [24]) [24, 26, 29, 31]
ZVEID <3> (<3> specific caspase 6 inhibitor [24]) [24]
ZVEID-fmk <3> (<3> caspase 6-specific inhibitor, reduces apoptosis and prevents periplakin cleavage in adherent cells, although it does not completely prevent cells from detaching [26]) [26]
acetyl-AEVD-aldehyde <3> [4]
acetyl-DEVD-aldehyde <3> [4]
acetyl-IETD-aldehyde <3> [4]
acetyl-Val-Ile-Asp-aldehyde <3> [20]
acetyl-WEHD-aldehyde <3> [4]
benzyloxycarbonyl-DRHD-fluoromethylketone <3> [16]
benzyloxycarbonyl-VAD-fluoromethylketone <3> (<3> $t_{1/2}$ at 0.001 mM is 98 s [4]) [4, 16]
benzyloxycarbonyl-VEID-fluoromethylketone <3> [16]
β-lactone <3> [25]
epoxomicin <3> [25]
lactacystin <3> [25]
siRNA <3> (<3> silencing of caspase-6 expression [31]) [31]
Additional information <3> (<3> K_i-value above 0.01 mM for acetyl-YVAD-aldehyde [4]) [4]

Activating compounds

adriamycin <3> (<3> increases caspase-6 mRNA levels in HCT116 p53+ and neo cells but not in E6 cells [30]) [30]
P53 <3> [30]
tumor necrosis factor α <3> (<3> activates caspase-6 which in turn cleaves transcription factor AP2α [16]) [16]

etopside <3> (<3> mild induction of the enzyme in HCT116 p53+ cells [30]) [30]
resveratrol <3> (<3> induces caspase-6-dependent cleavage of lamin A [31]) [31]

Turnover number (min^{-1})
Additional information <3> [18]

Specific activity (U/mg)
Additional information <4> (<4> VEID-7-amido-4-trifluoromethylcoumarin cleavage acitivity overall increases by 6.1fold between E15.5 and E18.5 rat embryos [25]) [25]

K_m-Value (mM)
0.03 <3> (acetyl-VEID-4-nitroanilide, <3> pH 7.5, 30°C [18]) [18]
0.16 <3> (acetyl-LEVD-4-nitroanilide, <3> pH 7.5, 30°C [18]) [18]
0.17 <3> (acetyl-VEHD-7-amido-4-methylcoumarin, <3> pH 7.0 or pH 7.5 [5]) [5]
0.18 <3> (acetyl-DEVD-4-nitroanilide, <3> pH 7.5, 30°C [18]) [18]
0.58 <3> (acetyl-VQVD-4-nitroanilide, <3> pH 7.5, 30°C [18]) [18]
1.2 <3> (acetyl-YEVD-4-nitroanilide, <3> pH 7.5, 30°C [18]) [18]
1.3 <3> (acetyl-DQMD-4-nitroanilide, <3> pH 7.5, 30°C [18]) [18]
7 <3> (acetyl-VDQQD-4-nitroanilide, <3> pH 7.5, 30°C [18]) [18]

K_i-Value (mM)
5.6e-006 <3> (acetyl-IETD-aldehyde, <3> pH 7.5, 25°C [4]) [4]
3.1e-005 <3> (acetyl-DEVD-aldehyde, <3> pH 7.5, 25°C [4]) [4]
5.2e-005 <3> (acetyl-AEVD-aldehyde, <3> pH 7.5, 25°C [4]) [4]
0.0013 <3> (cowpox serpin CrmA, <3> pH 7.5, 25°C [4]) [4]
0.003 <3> (acetyl-WEHD-aldehyde, <3> pH 7.5, 25°C [4]) [4]

pH-Optimum
7-7.5 <3> (<3> reaction with acetyl-VEHD-7-amido-4-methylcoumarin [5]) [5]

4 Enzyme Structure

Molecular weight
24000 <4> (<4> Western blot analysis, processed large subunit and the attached prodomain of caspase 6 [28]) [28]
Additional information <6> (<6> Mch2α transcript encodes the full-length Mch2, whereas the Mch2β transcript encodes a shorter Mch2 isoform, probably as a result of alternative slicing [9]) [9]

Subunits
dimer <3> (<3> procaspase 6, SDS-PAGE, chemical cross-linking and gel filtration, nearly identical CD spectra of rCaspase 6 and D316A caspase 6, indicating that overal structures of both precursor and mature forms of caspase 6 should be almost indistinguishable [22]) [22]

Posttranslational modification

proteolytic modification <3> (<3> the activation site is TEVD-/-(P4,P3,P2,P1) [7]; <3> viral nucleocapsid protein of transmissible gastroenteritis coronavirus triggers the processing of procaspase 6 in human rectal tumor cell line HRT18jap1 [12]; <3> caspase-6 is inactive until the short 23 amino acid prodomain is removed [11]) [7, 11, 12]

5 Isolation/Preparation/Mutation/Application

Source/tissue

DLD-1 cell <3> [30]
HCT-116 cell <3> (<3> variants p53+, p53-, Bax+, Bax- [31]) [30, 31]
HRT-18 cell <3> [12]
JURKAT cell <3, 6> (<3> fas-stimulated [20]) [9, 13, 20]
Jurkat E-61 cell <3> (<3> leukemic T cell line [11]) [11]
MDCK cell <3> [26]
SW-480 cell <3> [30]
T-cell <6> [9]
T-cell leukemia cell <3> [23]
alveolar cell <3> (<3> A549 cell line infected by unencapsulated Streptococcus pneumoniae type 2 strain R6x and capsulated Streptococcus pneumoniae strain D39 and the pneumolysin-deficient R6xply mutant [24]) [24]
brain <3, 7> (<7> low activity [10]) [10, 21, 27]
breast cancer cell <3> [16]
bronchial epithelial cell line <3> (<3> BEAS-2B cell line infected by unencapsulated Streptococcus pneumoniae type 2 strain R6x [24]) [24]
colorectal cancer cell line <3> [29]
dentate gyrus <4> (<4> in the inner molecular layer [28]) [28]
fiber <4> (<4> primary fiber cells [25]) [25]
heart <7> [10]
hippocampal pyramidal layer <4> (<4> CA1 and CA3a region [28]) [28]
kidney <7> [10]
lens <2, 4> [25]
leukemia cell <3> (<3> THP-1 human monocytic cell culture [25]) [25]
liver <7> [10]
lung <6, 7> [1, 10]
lung epithelium <3> [24]
lymphocyte <6> [2]
lymphoma cell <1> (<1> parental and caspase-6-DT40 chicken lymphoma cells [23]) [23]
neurofibrillary tangles <3> [21]
neuron <4> (<4> hilar neurons, in the somata and in dendrites [28]) [28]
prostate cancer cell <3> [23]
skeletal muscle <7> (<7> low activity [10]) [10]
spleen <7> [10]
testis <7> [10]

Additional information <3> (<3> p53 up-regulates caspase -6mRNA in H460, H460-neo, H460-E6, HCT16-neo, HCT16-E6, HCT16-P53-, SKBR3, U2OS, M3, HCC1937 and SW13 cell lines, MCF7 cells fail to show induction of caspase 6-mRNA [30]; <3> present in neurophil threads and neuritic plaques, not in the cerebellum [21]; <3> temporal and frontal cortex [21]) [21, 30]

Localization

nucleus <3, 4> [23, 25]
soluble <3> [11]
Additional information <3> (<3> active Csp-6 is not present in the nuclei of Alzheimer's disease neurons [21]) [21]

Purification

<3> [5, 11, 21, 26]
<3> (purified to homogeneity) [22]

Cloning

<3> [4, 5, 17]
<3> (cloned into pET-23 bacterial expression vector) [26]
<3> (expression in Escherichia coli) [22]
<3> (inserted into the pIVEX vector) [21]
<5> [3]
<6> [9]
<7> [10]

Engineering

D316A <3> (<3> to prevent autocatalytic processing of the specific site of procaspase 6, Asp316 of rCaspase 6 is replaced with Ala [22]) [22]
S257A <3> (<3> mutant caspase-6, not phosphorylated in the presence of active AMPK-related kinase 5 [29]) [29]
W175F <3> (<3> reduced autocatalytic processing activity [22]) [22]

Application

medicine <1, 2, 3, 4> (<4> caspase 6 expression remains elevated long after the occurrence of acute cell death during epileptogenesis and epilepsy, indicating that the enzyme has functions other than execution of programmed cell death in epileptogenic hippocampus [28]; <3> caspase-6 is active early in the pathogenesis of Alzheimer's disease, the enzyme is strongly implicated in human neuronal degeneration and apoptosis, its inhibition may be an efficient treatment [21]; <3> caspase-6 is phosphorylated by AMP-activated protein kinase related kinase 5 at Ser257 in colorectal cancer cells, leading to inactivation of caspase-6 and resulting in resistance to cell death via cFLIPs protection and leading to resistance to the FAS ligand/Fas system [29]; <3> caspase-6 is upregulated in response to p53 overexpression, induction of caspase-6 expression lowers the cell death threshold in response to apoptotic signals that activate caspase-6, potential mechanism of lowering the death threshold, which could be important for chemosensitization [30]; <3> critical role of caspase-6 and its cleavage of lamin A in apoptotic signaling triggered by resveratrol in the colon carcinoma cells [31]; <2,4> difference between

normal fiber cell differentation and apoptosis and the capacity of the lens to differentially regulate these two processes [25]; <3> role for caspase-6 and N-terminal truncation of tau during neurovibrillary tangle evolution and the progression of Alzheimer's disease [27]; <3> Streptococcus pneumoniae induces apoptosis of human alveolar and bronchial epithelial cells, programmed cell death is excecuted by caspase 6, and can be blocked by overexpression of Bcl2 [24]; <1> the loss of caspase-6 does not appear to impair the ability of any anticancer agents to induce apoptosis [23]) [21, 23, 24, 25, 27, 28, 29, 30, 31]

References

[1] Strausberg R.L.; Feingold E.A.; Grouse L.H.; Derge J.G., et al.: Generation and initial analysis of more than 15,000 full-length human and mouse cDNA sequences. Proc. Natl. Acad. Sci. USA, **99**, 16899-16903 (2002)
[2] Srinivasula, S.M.; Fernandes-Alnemri, T.; Zangrilli, J.; Robertson, N.; Armstrong, R.C.; Wang, L.; Trapani, J.A.; Tomaselli, K.J.; Litwack, G.; Alnemri E.S.: The Ced-3/interleukin 1β converting enzyme-like homolog Mch6 and the lamin-cleaving enzyme Mch2α are substrates for the apoptotic mediator CPP32. J. Biol. Chem., **271**, 27099-27106 (1996)
[3] Nakajima, K.; Takahashi, A.; Yaoita, Y.: Structure, expression, and function of the Xenopus laevis caspase family. J. Biol. Chem., **275**, 10484-10491 (2000)
[4] Garcia-Calvo, M.; Peterson, E.P.; Leiting, B.; Ruel, R.; Nicholson, D.W.; Thornberry, N.A.: Inhibition of human caspases by peptide-based and macromolecular inhibitors. J. Biol. Chem., **273**, 32608-32613 (1998)
[5] Garcia-Calvo, M.; Peterson, E.P.; Rasper, D.M.; Vaillancourt, J.P.; Zamboni, R.; Nicholson, D.W.; Thornberry, N.A.: Purification and catalytic properties of human caspase family members. Cell Death Differ., **6**, 362-369 (1999)
[6] Chang, H.Y.; Yang, X.: Proteases from cell suicide: functions and regulation of caspases. Microbiol. Mol. Biol. Rev., **64**, 821-846 (2000)
[7] Thornberry, N.A.; Rano, T.A.; Peterson, E.P.; et al.: A combinatorial approach defines specificities of members of the caspase family and granzyme B. Functional relationships established for key mediators of apoptosis. J. Biol. Chem., **272**, 17907-17911 (1997)
[8] van de Craen, M.; Berx, G.; van den Brande, I.; Fiers, W.; Declercq, W.; Vandenabeele, P.: Proteolytic cleavage of β-catenin by caspases: an in vitro analysis. FEBS Lett., **458**, 167-170 (1999)
[9] Fernandes-Alnemri, T.; Litwack, G.; Alnemri, E.S.: Mch2, a new member of the apoptotic Ced-3/Ice cysteine protease gene family. Cancer Res., **55**, 2737-2742 (1995)
[10] van de Craen, M.; Vandenabeele, P.; Declercq, W.; van den Brande, I.; van Loo, G.; Molemans, F.; Schotte, P.; van Criekinge, W.; Beyaert, R.; Fiers, W.: Characterization of seven murine caspase family members. FEBS Lett., **403**, 61-69 (1997)

[11] Cowling, V.; Downward, J.: Caspase-6 is the direct activator of caspase-8 in the cytochrome c-induced apoptosis pathway: absolute requirement for removal of caspase-6 prodomain. Cell Death Differ., **9**, 1046-1056 (2002)
[12] Eleouet, J.F.; Slee, E.A.; Saurini, F.; Castagne, N.; Poncet, D.; Garrido, C.; Solary, E.; Martin, S.J.: The viral nucleocapsid protein of transmissible gastroenteritis coronavirus (TGEV) is cleaved by caspase-6 and -7 during TGEV-induced apoptosis. J. Virol., **74**, 3975-3983 (2000)
[13] Galande, S.; Dickinson, L.A.; Mian, I.S.; Sikorska, M.; Kohwi-Shigematsu, T.: SATB1 cleavage by caspase 6 disrupts PDZ domain-mediated dimerization, causing detachment from chromatin early in T-cell apoptosis. Mol. Cell. Biol., **21**, 5591-5604 (2001)
[14] Mahoney, J.A.; Odin, J.A.; White, S.M.; Shaffer, D.; Koff, A.; Casciola-Rosen, L.; Rosen, A.: The human homologue of the yeast polyubiquitination factor Ufd2p is cleaved by caspase 6 and granzyme B during apoptosis. Biochem. J., **361**, 587-595 (2002)
[15] Nyormoi, O.; Wang, Z.; Doan, D.; Ruiz, M.; McConkey, D.; Bar-Eli, M.: Transcription factor AP-2α is preferentially cleaved by caspase 6 and degraded by proteasome during tumor necrosis factor α-induced apoptosis in breast cancer cells. Mol. Cell. Biol., **21**, 4856-4867 (2001)
[16] Nyormoi, O.; Wang, Z.; Bar-Eli, M.: Sequence-based discovery of a synthetic peptide inhibitor of caspase 6. Apoptosis, **8**, 371-376 (2003)
[17] Hill, J.; Duckworth, M.; Murdock, P.; Rennie, G.; Sabido-David, C.; Ames, R.S.; Szekeres, P.; Wilson, S.; Bergsma, D.J.; Gloger, I.S.; Levy, D.S.; Chambers, J.K.; Muir, A.I.: Molecular cloning and functional characterization of MCH2, a novel human MCH receptor. J. Biol. Chem., **276**, 20125-20129 (2001)
[18] Talanian, R.V.; Quinlan, C.; Trautz, S.; Hackett, M.C.; Mankovich, J.A.; Banach, D.; Ghayur, T.; Brady, K.D.; Wong, W.W.: Substrate specificities of caspase family proteases. J. Biol. Chem., **272**, 9677-9682 (1997)
[19] Samejima, K.; Svigen, P.A.; Basi, G.S.; Kottke, T.; Mesner, P.W.; Stewart, L.; Durrieu, F.; Poirier, G.G.; Alnemri, E.S.; Champoux, J.J.; Kaufmann, S.H.; Earnshaw, W.C.: Caspase-mediated cleavage of DNA topoisomerase I at unconventional sites during apoptosis. J. Biol. Chem., **274**, 4335-4340 (1999)
[20] Hirata, H.; Takahashi, A.; Kobayashi, S.; Yonehara, S.; Sawai, H.; Okazaki, T.; Yamamoto, K.; Sasada, M.: Caspases are activated in a branched protease cascade and control didtinct downstream processes in fas-induced apoptosis. J. Exp. Med., **187**, 587-600 (1998)
[21] Guo, H.; Albrecht, S.; Bourdeau, M.; Petzke, T.; Bergeron, C.; LeBlanc, A.C.: Active caspase-6 and caspase-6-cleaved tau in neuropil threads, neuritic plaques, and neurofibrillary tangles of Alzheimer's disease. Am. J. Pathol., **165**, 523-531 (2004)
[22] Kang, B.H.; Ko, E.; Kwon, O.K.; Choi, K.Y.: The structure of procaspase 6 is similar to that of active mature caspase 6. Biochem. J., **364**, 629-634 (2002)
[23] Loegering, D.A.; Ruchaud, S.; Earnshaw, W.C.; Kaufmann, S.H.: Evaluation of the role of caspase-6 in anticancer drug-induced apoptosis. Cell Death Differ., **13**, 346-347 (2006)

[24] Schmeck, B.; Gross, R.; N'Guessan, P.D.; Hocke, A.C.; Hammerschmidt, S.; Mitchell, T.J.; Rosseau, S.; Suttorp, N.; Hippenstiel, S.: Streptococcus pneumoniae-induced caspase 6-dependent apoptosis in lung epithelium. Infect. Immun., **72**, 4940-4947 (2004)
[25] Foley, J.D.; Rosenbaum, H.; Griep, A.E.: Temporal regulation of VEID-7-amino-4-trifluoromethylcoumarin cleavage activity and caspase-6 correlates with organelle loss during lens development. J. Biol. Chem., **279**, 32142-32150 (2004)
[26] Kalinin, A.E.; Kalinin, A.E.; Aho, M.; Uitto, J.; Aho, S.: Breaking the connection: caspase 6 disconnects intermediate filament-binding domain of periplakin from its actin-binding N-terminal region. J. Invest. Dermatol., **124**, 46-55 (2005)
[27] Horowitz, P.M.; Patterson, K.R.; Guillozet-Bongaarts, A.L.; Reynolds, M.R.; Carroll, C.A.; Weintraub, S.T.; Bennett, D.A.; Cryns, V.L.; Berry, R.W.; Binder, L.I.: Early N-terminal changes and caspase-6 cleavage of tau in Alzheimer's disease. J. Neurosci., **24**, 7895-7902 (2004)
[28] Narkilahti, S.; Pitkanen, A.: Caspase 6 expression in the rat hippocampus during epileptogenesis and epilepsy. Neuroscience, **131**, 887-897 (2005)
[29] Suzuki, A.; Kusakai, G.; Kishimoto, A.; Shimojo, Y.; Miyamoto, S.; Ogura, T.; Ochiai; A.; Esumi, H.: Regulation of caspase-6 and FLIP by the AMPK family member ARK5. Oncogene, **23**, 7067-7075 (2004)
[30] MacLachlan, T.K.; El-Deiry, W.S.: Apoptotic threshold is lowered by p53 transactivation of caspase-6. Proc. Natl. Acad. Sci. USA, **99**, 9492-9497 (2002)
[31] Lee, S.C.; Chan, J.; Clement, M.V.; Pervaiz, S.: Functional proteomics of resveratrol-induced colon cancer cell apoptosis: caspase-6-mediated cleavage of lamin A is a major signaling loop. Proteomics, **6**, 2386-2394 (2006)