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Editorial

Death by a thousand cuts: an ever increasing list of caspase substrates

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At present, mammalian caspases comprise a group of at least 13 protease members which either generate mature pro-inflammatory cytokines or promote apoptosis (Cohen, 1997; Nicholson and Thornberry, 1997; Van de Craen *et al*, 1997; Humke *et al*, 1998; Schulze-Osthoff *et al*, 1998). Based on phylogenetic analysis and positional scanning studies of their peptide substrates, caspases can be divided into three subfamilies: The ICE-like protease family includes caspase-1, -4, -5 and -13 as well as murine caspase-11 and -12, for which no human equivalents have yet been identified. The Ced-3 subfamily includes caspase-3, -6, -7, -8, -9 and -10, whereas the third subfamily consists of only one member, caspase-2. Within each subfamily, the peptide sequence preferences in the substrates are remarkably similar or even identical. This demonstrates that, at least in some cases, different caspases can cleave the same substrates, suggesting some degree of functional redundancy within the caspase family.

Central to the understanding of the molecular mechanism of cell death is the identification of caspase targets and the elucidation of the consequences of proteolytic cleavage. Thus far, more than 60 proteins have been found to be cleaved by caspases, and new substrates are continuously being identified (Table 1). Given the great number of different caspases, the list of substrates is still relatively small. For most proteins, the consequences of cleavage are poorly understood. In a few cases, however, proteolysis of certain components can be linked to discrete morphological changes of cell death.

Which requirements should an apoptosis-relevant caspase substrate meet? Because apoptosis is an ordered sequence of rather stereotypical alterations in every cell type, one would predict that caspase substrates should be ubiquitously expressed and evolutionary conserved, at least in their aspartate cleavage site. The known substrates of caspases can be loosely categorized into a few functional groups including proteins involved in scaffolding of the cytoplasm and cell nucleus, signal transduction and transcription-regulatory proteins, cell-cycle controlling components and proteins involved in DNA replication and repair. In addition, activation of members of the first subfamily of caspases, caspase-1 and presumably caspase-4 and -5, results in the processing of cytokine precursors, which are presumably not directly involved in cell death.

While some substrates are functionally inactivated upon caspase-mediated cleavage, other proteins and enzymes can be activated, mostly by cleavage of an inhibitory or regulatory domain within the caspase target. In most cases the physiological consequence of this gain-of-function cleavage for apoptosis remains unclear. Caspase-mediated cleavage should result in different net effects: (i) a halt of cell cycle progression, (ii) disabling of repair mechanisms, (iii) disassembly of molecular structures, (iv) cell detachment, and (v) tagging of the apoptotic cell for engulfment by phagocytes.

A number of structural proteins in the cell nucleus and cytoplasm have been identified to be cleaved by caspases, such as actin, fodrin, catenins, keratins, Gas2 and lamins (for references see Cohen, 1997; Nicholson and Thornberry, 1997; Porter *et al*, 1997; Tan and Wang, 1998; Cryns and Yuan, 1998). Degradation of lamin B which is predominantly mediated by caspase-6 may lead to the disassembly of the nuclear envelope and the final collapse of the cell nucleus (Rao *et al*, 1996). In contrast, cleavage of gelsolin, a cytoplasmic actin-severing protein, may contribute to membrane blebbing and other morphological features of the apoptotic phenotype. Gelsolin is cleaved by caspase-3 to generate a constitutively active fragment that can depolymerize F-actin (Kothakota *et al*, 1997). Interestingly, gelsolin-deficient cells show a strong delay in membrane blebbing when exposed to apoptotic stimuli. It has been also reported that actin can be directly cleaved by caspases in pheochromocytoma and ovarian carcinoma cells (Kayalar *et al*, 1996; Chen *et al*, 1996), whereas in many other cell types no cleavage could be detected (Song *et al*, 1997). Thus, it is possible that certain protein cleavages may be cell type-specific which may also due to variations in the expression of individual caspases in different cell types. Activation of caspases may be not only required for destruction of the cell's architecture, but also necessary for the detachment and clearance of an apoptotic cell from the embedding tissue. Indeed, some caspase substrates participate in cell adhesion, such as β-catenin, plakoglobin and focal adhesion kinase (Brancolini *et al*, 1997; 1998; Herren *et al*, 1998; Crouch *et al*, 1996; Levkau *et al*, 1998a).

A strikingly large number of caspase targets are involved in cell cycle regulation and DNA repair mechanisms. One of the first death substrates found to be cleaved by caspases was poly(ADP-ribose)polymerase (PARP), which catalyzes the transfer of ADP-ribose polymers to nuclear proteins (Tewari *et al*, 1995). As DNA strand breaks activate the enzyme, PARP has been proposed to trigger DNA damage-induced apoptosis by depleting NAD stores. On the other hand, due to its role in DNA repair, cleavage of PARP may

Table 1 Caspase substrates

Cytoskeletal and structural proteins	
• Fodrin	Cortical cytokeleton
• β-Catenin	Cell adhesion
• Plakoglobin[1,2]	Cell adhesion
• Actin	Cytoskeleton
• Gelsolin	Actin-severing protein
• Keratin-18, −19	Intermediate filaments
• Gas2	Microfilament organization
• Lamins	Nuclear envelope
Cell cycle and replication	
• Topolsomerase-I	DNA replication
• MCM3 nuclear replication factor[3]	DNA replication
• DNA replication complex C (DSEB/RFC140)	DNA replication
• MDM2/HDM2	Inhibitor of p53
• NuMA	Nuclear mitosis apparatus protein
• Retinoblastoma protein (Rb)	Assembly of the repressor complex
• p21 (Cip1/Waf1)[4]	Cdk2 inhibitor
• p27 (Kip1)[4]	Cdk inhibitor
• Wee 1[5]	Kinase, Cdc2 inhibitor
• Cdc27[5]	Anaphase-promoting complex
• Cyclin A	Mitosis
Transcription and translation	
• Sterol-regulatory element-binding proteins (SREBPs)	Cholesterol metabolism
• STAT1[5]	Signal transduction of cytokines
• NF-κB (p50, p65)[7]	Cytokine and anti-apoptotic genes
• IκB-α	Inhibitor of NF-κB
• Sp1	Transcription factor
• U1-70 kD sRNP	Pre-mRNA splicing
• Heteronuclear ribonuclear proteins (hnRNPs C1/2)	Pre-mRNA splicing
DNA cleavage and repair	
• Poly (ADP-ribose) polymerase (PARP)	DNA repair
• DNA-dependent protein kinase (DNA-PK)	DNA repair
• Inhibitor of caspase-activated DNase (ICAD, DFF)	DNA cleavage
Protein kinases in signal transduction	
• Protein kinase Cδ	Signal transduction
• Protein kinase Cθ	Signal transduction
• PKC-related kinase-2 (PRK2)	Signal transduction
• MEKK-1	MAP kinase pathway
• p21-activated kinase (PAK2, hPAK65)	MAP kinase pathway
• PITSLRE kinases	Cell cycle regulation
• Focal adhesion kinase	Cell adhesion
• MST/krs[8,9]	STE20-related kinase
• Calmodulin-dependent kinase IV[10]	Signal transduction
Other signal transducers	
• Protein phosphatase 2A (PP2A)[11]	Signal transduction
• D4-GDP dissociation inhibitor (D4-GDI)	Inhibitor of small GTPases, Rho pathway
• Ras GAP[12,13]	Ras GTPase activating protein
• p28 Bap31	Bcl-2 adaptor of the endoplasmic reticulum
• cytosolic PLA_2	Phospholipid metabolism
Cytokine precursors	
• Pro-interleukin-1β	Immune regulation
• Pro-interleukin-16[14]	Immune regulation
• Pro-interleukin-18 (IFN-γ-inducing factor)	Immune regulation
Others	
• Pro-caspases	
• Rabaptin-5	Endosome fusion
• Calpastatin[15,16]	Calpain inhibitor
• Nedd4[17]	Ubiquitin protein ligase
• Bcl-2	Apoptosis inhibitor
• Bcl-x_L	Apoptosis inhibitor
• Bid[18,19]	Apoptosis activator
• hsp90[20]	Heat-shock protein
• APC protein[21]	Adenomatous polyposis coli protein
• Huntingtin	Involved in Huntington's disease
• Atrophin-1[22]	Involved in neurodegeneration
• Ataxin-3[22]	Involved in neurodegeneration
• DRPLA-protein[23]	Involved in neurodegeneration
• Presenilins	Involved in Alzheimer's disease

For a partial list of references the reader is referred to Cohen 1997; Nicholson and Thornberry, 1997; Porter *et al*, 1997; Tan and Wang, 1998; Cryns and Yuan ,1998. Non-cited and very recently identified caspase substrates are published in [1]Herren *et al*, 1998; [2]Brancolini *et al*, 1998; [3]Schwab *et al*, 1998; [4]Levkau *et al*, 1998b; [5]Zhou *et al*, 1998; King and Goodbourn, 1998; [7]Ravi *et al*, 1998; [8]Graves *et al*, 1998; [9]Lee *et al*, 1998; [10]McGinnis *et al*, 1998; [11]Santoro *et al*, 1998; [12]Widmann *et al*, 1998; [13]Wen *et al*, 1998; [14]Zhang *et al*, 1998; [15]Porn-Ares *et al*, 1998; [16]Wang *et al*, 1998; [17]Harvey *et al*, 1998; [18]Luo *et al*, 1998; [19]Li *et al*, 1998; [20]Prasad *et al*, 1998; [21]Browne *et al*, 1998; [22]Wellington *et al*, 1998. [23]DRPLA,dentarorubral pallidoluysian atrophy

compromise most of its DNA repair activity, and thus may contribute to the demise of the cell. However, $PARP^{-/-}$ mice neither reveal a phenotype which would indicate a crucial role in apoptosis nor is the sensitivity towards CD95- and TNF-R1-mediated apoptosis affected (Wang *et al*, 1997). Thus, cleavage of PARP may be a characteristic event or a bystander effect, but is presumably dispensable for most apoptotic pathways.

Retinoblastoma protein (RB) and the mouse double minute-2 protein (MDM2) are other examples of caspase substrates involved in repair mechanisms and cell cycle regulation (Jänicke *et al*, 1996; Erhardt *et al*, 1997). MDM2 normally retains p53 in the cytoplasm, and cleavage may allow p53 entry into the nucleus to induce cell cycle arrest or apoptosis. However, since apoptosis also occurs in enucleated cells, cleavage of nuclear proteins may be not essential for all apoptotic processes. It has been furthermore reported that cyclin A is cleaved during apoptosis of *Xenopus* oocytes after treatment with hydroxyurea or cycloheximide (Stack and Newport, 1997). However, the caspase cleavage site of cyclin A is not conserved in mammalian cells, and the protein is not cleaved in a variety of apoptotic systems. Thus, one should not generalize a reported caspase substrate for all species.

An increasing number of recently identified caspase substrates are protein kinases or other proteins involved in signal transduction. In many cases, caspase cleavage results in the removal of a regulatory protein domain generating a constitutively active kinase. For instance, proteolytic activation of the p21-activated kinase PAK2 has been reported during CD95 and TNF-mediated apoptosis (Rudel and Buckoch, 1997). As PAK2 is able to trigger stress-activated kinases of the JNK/SAPK pathway, this may provide a link between caspases and JNK/SAPK activation during apoptosis signaling. Interestingly, blocking the activity of PAK2 by a dominant-negative mutant led to the inhibition of formation of apoptotic bodies, whereas nuclear apoptosis and phosphatidylserine externalization remained unaffected. Therefore, the cleavage of PAK2 is an example of how different features of apoptosis might be discriminated at the level of caspase targets.

The activation of certain proteins by caspases is mediated by a rather limited and specific endoproteolytic cleavage, which is a general feature of caspase activity. Among other enzymes activated by caspases are cytosolic phospholipase A_2, protein kinases such as MEKK-1, MST, the PKC isoforms delta and theta, PKC-related kinase-2, and transcription factors such as the sterol-regulatory element binding protein (SREBP)-1 and -2. It still remains to be established, whether caspase-mediated activation of one of these molecules is involved in transduction of the apoptotic signal. It has been also observed that anti-apoptotic proteins of the Bcl-2 family are cleaved by caspases (Cheng *et al*, 1997; Clem *et al*, 1998). This cleavage results in their conversion to pro-apoptotic proteins which may similar act to Bax and thereby amplify an apoptotic signal. Similarly, it has been observed that during death receptor-mediated apoptosis caspase-8 can cleave the Bcl-2 member Bid into an active C-terminal fragment that induces the pro-apoptotic release of cytochrome c from mitochondria (Luo *et al*, 1998; Li *et al*, 1998). A caspase-mediated activation of cellular functions has been recently provided by the identification of a novel murine endonuclease, designated CAD for caspase-activated DNase (Enari *et al*, 1998). CAD is sequestered in the cytosol as a latent form by binding to the inhibitory subunit, called ICAD, whose human homologue has been previously identified as DNA fragmentation factor (DFF) (Liu *et al*, 1997). Upon induction of apoptosis, ICAD/DFF is cleaved by caspase-3, which allows the DNase to translocate to the nucleus and to degrade DNA. Interestingly, overexpression of ICAD blocks chromatin changes of apoptosis but does not abrogate other morphological alterations.

The cleavage of some substrates can be directly linked to the pathogenesis of certain diseases. Huntington's disease, a genetically determined neurodegenerative disease, results from the expansion of CAG triplets at the 5′-primed end of the gene encoding huntingtin, a protein with a long polyglutamine stretch. Huntingtin is cleaved by caspase-3 and results in an N-terminal fragment which is directly cytotoxic for neurons (Goldberg *et al*, 1996). Huntington's disease manifests only when huntingtin exceeds 35 glutamine residues. Because the rate of caspase cleavage of huntingtin correlates with the length the polyglutamine stretch, accumulation of the fragment may cause a vicious cycle. It is interesting to note that, although mutated huntingtin is ubiquitously expressed, the genetic lesion is associated with apoptosis only in certain brain regions. A pathogenic role of caspase cleavage has been also implicated in other neurodegenerative disorders. Similar to huntingtin, the polyglutamine tract proteins atrophin-1, ataxin-3 and DRPLA-protein are caspase substrates (Wellington *et al*, 1998; Miyashita *et al*, 1997). The cytotoxic properties of their cleavage products illustrate that specific caspase substrates may be not only involved in the destruction of the cell, but also fulfil an active role in the exacerbation of the apoptotic process.

Is there a single caspase substrate whose cleavage is critical or relatively more important for cell death? It should be pointed out that thus far none of the cleavage events has been shown to be absolutely required to kill cells. Although ectopic overexpression of non-cleavable mutants (for example of Rb, PAK-2 or MEKK-1) delays some forms of apoptosis or inhibits certain morphological features of cell death, in any case, final cell death could not be prevented. This is in contrast to the effect of pharmaceutical caspase inhibitors and may suggest that a critical death substrate might not have been identified yet. More likely, however, is that apoptosis requires 'a thousand cuts' (Martin and Green, 1995), each contributing to a part of the apoptotic phenotype. The cleavage of multiple substrates with key homeostatic and structural functions may then collectively culminate in the systematic and orderly disassembly of the apoptotic cell.

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(Owing to space limitations, the authors apologize that many articles which significantly contributed to the elucidation of caspase substrates could not be cited.)

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