Review

Many cuts to ruin: a comprehensive update of caspase substrates

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Abstract

Apoptotic cell death is executed by the caspase-mediated cleavage of various vital proteins. Elucidating the consequences of this endoproteolytic cleavage is crucial for our understanding of cell death and other biological processes. Many caspase substrates are just cleaved as bystanders, because they happen to contain a caspase cleavage site in their sequence. Several targets, however, have a discrete function in propagation of the cell death process. Many structural and regulatory proteins are inactivated by caspases, while other substrates can be activated. In most cases, the consequences of this gain-of-function are poorly understood. Caspase substrates can regulate the key morphological changes in apoptosis. Several caspase substrates also act as transducers and amplifiers that determine the apoptotic threshold and cell fate. This review summarizes the known caspase substrates comprising a bewildering list of more than 280 different proteins. We highlight some recent aspects inferred by the cleavage of certain proteins in apoptosis. We also discuss emerging themes of caspase cleavage in other forms of cell death and, in particular, in apparently unrelated processes, such as cell cycle regulation and cellular differentiation.

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Abbreviations: See Table 1

Introduction

In 1998, we published a list of caspase substrates comprising 65 different proteins that were cleaved by proteases of the caspase family.1 Most of the substrates known at that time could be categorized into a few functional groups, including proteins involved in scaffolding of the cytoplasm and nucleus, signal transduction and transcription-regulatory proteins, cell cycle controlling components and proteins involved in DNA replication and repair. Since then, the number of caspase substrates has considerably increased, more recently in particular because of a systematic proteome analysis of apoptotic cells.2-4 To date, more than 280 caspase targets are identified. Various methods have been employed to search for caspase substrates, including direct cDNA pool expression strategies or two-hybrid cloning approaches.5,6 By comparative two-dimensional (2D) gel electrophoresis of healthy and apoptotic cells, often a few hundred altered protein spots can be detected. Although not all of them have been confirmed as caspase targets, such proteomic approaches will certainly lead to the identification of numerous additional substrates in the near future (Table 1).

Already now, a bewildering number of substrates are cleaved by caspases. However, it should be kept in mind that some proteins might be cleaved very late and less completely during apoptosis, or not in all cell types. For example, it has been reported that α-actin can be cleaved by caspases in pheochromocytoma and ovarian carcinoma cells,7,8 whereas in many other cell types no cleavage was detected.9 Thus, it is possible that certain protein cleavages are cell type-specific, which may be because of variations in the expression of individual caspases. Also, caspase cleavage sites are not always conserved in different species. For instance, cyclin A is cleaved during apoptosis of Xenopus oocytes,10 but the caspase cleavage site is not present in homologues of mammalian cells. Some proteins, such as DNase-X, contain one or more classical cleavage sites in their sequence. However, the protein is virtually not cleaved inside apoptotic cells despite massive caspase activation.11 Moreover, in some cases, a first cut by caspases unleashes additional cleavage sites for other types of proteases. Cleavage of acinus, for instance, by caspase-3 is necessary but not sufficient to activate its DNA-condensing activity. For full activation, an additional, still unknown serine protease has to intervene. Only the combined action of both proteases generates the mature fragment, which, when added to purified nuclei, causes chromatin condensation.12

For many of the identified substrates, the functional consequences of their cleavage are unknown and have only been inferred from their normal functions. In other cases, the role of caspase cleavage has been experimentally assessed by expressing substrate proteins that have mutant caspase cleavage sites or by expressing protein fragments of the caspase-cleaved products. Given the high conservation of the apoptotic phenotype, from worms to mammals, it is highly likely that a conserved group of crucial caspase substrates exist. Proteolysis of the latter substrates presumably leads to the stereotypical destructive alterations that we call apoptosis.
| Substrate   | Physiological Function | Cleavage Effect | Consequences of Cleavage                                                                 | Cleavage Sites | References |
|------------|------------------------|----------------|--------------------------------------------------------------------------------------------|----------------|------------|
| **1. Apoptosis regulators** |                        |                |                                                                                           |                |
| Apaf-1     | Apoptosome component   | Inactivated?   | Cleavage product proapoptotic, if overexpressed                                           | SVTD (271)     | 43, 44     |
| Bad        | Proapoptotic Bcl-2 protein | Activated     | Cleavage product proapoptotic, if overexpressed                                           |                | 45         |
| Bax        | Proapoptotic Bcl-2 protein | Inactivated   | Generation of a proapoptotic fragment                                                     | FIQD (33)      | 46, 47     |
| Bcl-xL     | Apoptosis inhibitor    | Inactivated    | Generation of a proapoptotic fragment                                                     | HLDAD (61), SSLD (76) | 49, 50   |
| Bid        | Apoptosis inhibitor    | Inactivated?   | Generation of a proapoptotic fragment that is myristoylated; phosphorylation inhibits cleavage | LQTD (59)      | 14, 16, 51, 52 |
| c-FLIP     | Caspase-8 inhibitor    | Inactivated    | Generation of a proapoptotic fragment                                                     | LEVD (376)     | 53         |
| c-IAP1     | Caspase inhibitor      | Inactivated    | Generation of a proapoptotic fragment                                                     | ENAD (372)     | 54         |
| Procaspsases | Procaspsase-1-14     | Activated      | Activation by proteolytic processing                                                       | XXXD           | For a review see Earnshaw et al.55 |
| XIAP       | Caspase inhibitor      | Inactivated?   | Cleavage product proapoptotic                                                              | SESD (242)     | 56, 57     |
| **2. Cell adhesion** |                      |                |                                                                                           |                |
| APC        | Adenomatous polyposis cell protein | Inactivated  | Cleavage separates β-catenin binding region and N-terminal armadillo repeat               | DNID (777)     | 58, 59     |
| CALM       | Clathrin assembly protein of myeloid leukemia (syn. AP180), promotes assembly of clathrin triskelia into clathrin cages | Inactivated |                                                                                           | Unknown        | 60         |
| Cas        | Crk-associated substrate (p130cas), associates with FAK, pxlaxlin, involved in integrin signaling | Inactivated | Contributes to disassembly of focal adhesion complexes, interrupts extracellular survival signals | DVPD (416), DSPD (748) | 61, 62     |
| β/-Catenin | Cell adhesion and WNT/wingless signaling pathway, constituent of adherens junctions | Inactivated | Reduced β-catenin binding and cell–cell contact, reduced transcriptional activity, relocalization to the cytoplasm | SYLD (92), ADID (83), TQFD (115), YPVD (781), DLMD (764) | 61, 63–65 |
| γ/-Catenin | Adherens junction protein (syn. plakoglobin) | Inactivated | Relocalization to the cytoplasm, involved in cell dismantling | Unknown | 61, 64, 66 |
| Desmoglein-3 | Major transmembrane component of desmosomes | Inactivated | Loss of cell–cell contacts | DYAD (781) and additional unknown sites | 67         |
| Desmocolin 3 | Component of desmosomes | Inactivated | Loss of cell–cell contacts | Unknown | 67         |
| Desmoplakin | Desmoplakin-1, -2, components of desmosomes | Inactivated | Loss of cell–cell contacts | Unknown | 67         |
| E-cadherin | Calcium-dependent adhesion protein in adherens junctions | Inactivated | Rather late cleavage may contribute to disruption of cell–cell contacts | DTRD (750)     | 68, 69     |
| N-cadherin | Calcium-dependent cell adhesion protein | Inactivated | Rather late cleavage may be involved in loss of cell–cell contacts | Unknown | 70         |
| P-cadherin | Cell adhesion protein in adherens junctions | Inactivated? | Rather late cleavage may be involved in loss of cell–cell contacts | Putative site: ETAD (695) | 69         |
| FAk        | Focal adhesion kinase, tyrosine kinase involved in formation of contact sites to extracellular matrix | Inactivated | Cleavage leads to disassembly of the focal adhesion complex, cell detachment and interruption of survival signals | DOTD (772) | 71–74     |
| HEF1       | Human enhancer of filamentation 1, member of the docking protein family, involved in integrin signaling | Inactivated | Disruption of antiapoptotic integrin signaling | DLVD (363), DDDY (630) | 75, 76     |
| Connexin 43.6 | Lens gap junction protein | Inactivated | Cleavage at a noncanonical site; phosphorylation by casein kinase II prevents degradation | DEVE (367)     | 77         |
| Paxillin   | Component of the focal adhesion complex | Inactivated | Cleavage results in focal adhesion disassembly and detachment | Early: NQPD (102), SLD (301), Late: DLD (5), SLD (146), FPAD (165), SSLD (222) | 78, 79      |
| Plakophilin-1 | Component of desmosomes | Inactivated | Loss of cell–cell contacts | Unknown | 67         |
| **3. Cytoskeletal and structural proteins** |                        |                |                                                                                           |                |
| α-Actin    | Cardiac actin, myofilament protein | Inactivated | Rather inefficient cleavage by caspase-3, involved in myofibrillar damage | Unknown | 80         |
4. Nuclear structural and abundant proteins

| Substrate | Physiological Function | Cleavage Effect | Consequences of Cleavage | Cleavage Sites | References |
|-----------|------------------------|-----------------|--------------------------|----------------|------------|
| vMLC      | Ventricular essential myosin light chain, cardiac myofilament protein | Inactivated? | Cleavage dissociates the actin binding from the SH3 domain and leads to cytoskeletal reorganisation | EHID (361) | 84 |
| p150( ) | Mediates dynein/dynactin interaction | Inactivated | Cleavage destroys the cytoplasmic dynein complex and stops dynein-dependent membrane motility | Unknown | 83 |
| Plectin   | Abundant crosslinking protein of cytoplasmic filament systems Component of the membrane cortical cytoskeleton | Inactivated | Cleavage results in disruption of the cortical cytoskeleton and may contribute to membrane blebbing | DQTD (403) | 82, 93 |
| Tau       | Neuronal microtubule-associated protein | Inactivated | Cleavage generates a proapoptotic fragment, may be involved in neuronal disorders | DMVD (421) | 101, 102 |
| Troponin T| Cardiac troponin, myofilament protein | Inactivated | Cleavage contributes to myofibrillar damage and contractile dysfunction | VDFD (96) | 80 |
| 1.5-Microtubulin | Component of microtubuli | Inactivated? | Cleavage results in disruption of the cortical cytoskeleton and may contribute to membrane blebbing | Unknown | 3 |
| Vimentin  | Intermediate filament specific for mesenchymal cells | Inactivated | Disruption of intermediate filaments and promotion of apoptosis | DSVD (85), IDVD (259), TNLD (429) | 103, 104 |

**References**
- U Fischer et al. (2018). *Cell Death and Differentiation*
### 5. ER and Golgi-resident proteins

| Substrate | Physiological Function | Cleavage Effect | Consequences of Cleavage | Cleavage Sites<sup>a</sup> | References |
|-----------|------------------------|-----------------|--------------------------|-----------------------------|------------|
| p28BAP31 | Bcl-2 adaptor at the ER, originally identified as B-cell receptor-associated protein | Inactivated | BAP31 is cleaved by and recruits caspase-8 to the ER. Expression of cleaved product is proapoptotic and causes disturbed transport of proteins from ER to Golgi | AAVD (164) | 117–119 |
| Golgin-160 | Golgi autoantigen, Golgin-3 (GOLGA3), located at the rims of cisternae | Inactivated | Cleavage by caspase-2 results in disintegration of the Golgi complex | ESPD (59), CSTD (139), SEVT (311) | 120 |
| GRASP65 | Golgi reassembly and stacking protein of 65 kDa | Inactivated | Golgi disassembly and loss of integrity | SLLD (320), SFPD (375), TLPD (393) | 121 |
| Kinectin | ER-resident receptor for molecular motor kinesin, involved in microtubule-based vesicle transport | Inactivated | Preferentially cleaved by caspase-7 | Unknown | 122 |

### 6. Cell cycle

| Substrate | Physiological Function | Cleavage Effect | Consequences of Cleavage | Cleavage Sites<sup>a</sup> | References |
|-----------|------------------------|-----------------|--------------------------|-----------------------------|------------|
| c-Abl | Tyrosine kinase involved in cell cycle arrest | Inactivated | Cleavage-mediated inactivation may suppress erythropoiesis | Putative sites: DTTD (546), DTAD (655) | 123 |
| Bcr-Abi | Constitutively active fused gene product of c-Abi and Bcr in chronic myeloid leukemia | Inactivated | See c-Abl | 123 |
| Cdc6 | Required for prereplicative complex formation | Inactivated | Cleavage results in loss of chromatin binding | LVRD (99), SEVD (442) | 124 |
| CDC27 | Cdc2 and Cdk-inhibitory kinase of the anaphase-promoting complex | Inactivated | Cleavage results in increased Cdk activity | Unknown | 35 |
| Cyclin A | Xenopus cyclin A | Inactivated | The cleavage site of Xenopus Cyclin A2 is not present in mammals | DEPD (90) | 10 |
| Cyclin E | Regulator of G1/S cell cycle progression | Inactivated | Elimination of Cdk2 interaction, results in inactivation of cdk kinase. Overexpression of the p18 fragment triggers apoptosis | Unknown | 125 |
| MDM2/HDM2 | Mouse/human double minute chromosome oncogene 2, controls degradation of p53 | Inactivated | The cleaved MDM2 loses the ability to promote p53 degradation and functions in a dominant-negative fashion to stabilize p53 | DVPD (361) | 126, 127 |
| MDMX | p53-binding protein homologous to MDM2, which promotes degradation of p53. | Inactivated | In analogy to MDM2, cleaved MDMX does not degrade p53 and functions in a dominant-negative fashion to stabilize p53 | DVPD (361) | 128 |
| NuMA | Nuclear mitosis apparatus protein, translocates to spindle poles at mitosis | Inactivated | Cleavage causes redistribution of NuMA and contributes to nuclear disruption | DSDL (1712) | 129, 130 |
| p21<sub>Waf1</sub> | Cdk2 inhibitor involved in G1/S arrest | Inactivated | Loss of N-terminal cdk-inhibitory domain results in a reduced association with cyclin-cdk2 complexes and increased cdk2 activity | DHVD (112) | 131, 132 |
### Table 1 (continued)

| Substrate | Physiological Function | Cleavage Effect | Consequences of Cleavage | Cleavage Sites<sup>a</sup> | References |
|-----------|------------------------|-----------------|--------------------------|--------------------------|------------|
| p27<sup>Kip1</sup> | Cdk2 inhibitor | Inactivated | Cleavage results in reduced association with cyclin-cdk2 complexes and increased cdk2 activity | DPSD (139), ESQD (108) | 132, 133 |
| PITSLRE | Cell cycle-regulatory cdc2-like kinase | Activated? | Several isoforms are cleaved and presumably activated | YVPD (391) | 134, 135 |
| Prothymosin-α | Involved in cell proliferation | Inactivated | Cleavage prevents nuclear localization, proliferation-inducing ability is abolished | Three overlapping sites at the C-terminus: DDEDDVD(101) | 136, 137 |
| Rb | Retinoblastoma protein, phosphorylation-controlled cell cycle regulator that binds to E2F-1 | Inactivated | Rb is cleaved in its hypophosphorylated form which results in unopposed E2F-1 action and reduced antiapoptotic activity | DEAD (886) | 138 |
| Wee1 | Inhibitory kinase of cdc2 and cdk2 | Inactivated | Cleavage-mediated inhibition results in elevated cdk activity | Unknown | 35 |

#### 7. DNA synthesis, cleavage and repair

| Substrate | Physiological Function | Cleavage Effect | Consequences of Cleavage | Cleavage Sites<sup>a</sup> | References |
|-----------|------------------------|-----------------|--------------------------|--------------------------|------------|
| Acinus | 'Apoptotic chromatin condensation inducer in the nucleus' | Activated | Essential mediator of chromatin condensation | DELD (1093) | 12 |
| ATM | Ataxia telangiectasia mutated protein; kinase involved in the p53 DNA repair pathway | Inactivated | Cleavage abrogates kinase activity. Fragment is DNA binding and functions as a dominant-negative inhibitor | DYPD (863) | 139 |
| BLM | RECQ-like helicase, defective in Bloom's syndrome, involved in DNA replication and repair | Inactivated | Dominant-negative inhibitor | TEVD (415) | 140, 141 |
| BRCA-1 | Breast cancer suppressor protein, mediates cell cycle arrest and DNA repair | Inactivated | Interaction with topoisomerase III is impaired | DLLD (1154) | 142 |
| DNA-PKcs | DNA-dependent protein kinase catalytic subunit; involved in repair of DNA breaks and nucleotide excision repair | Inactivated | Loss of catalytic activity | DEVD (2713) | 143, 144 |
| ICAD | Inhibitor of caspase-activated DNase (syn. DFF45) | Inactivated | Cleavage liberates the active CAD endonuclease | DETD (117), DAVD (224) | 145, 146 |
| Helicard | CARD-containing DNA helicase | Activated | Involved in chromatin remodeling. Cleavage separates the CARD from the helicase domain and induces nuclear translocation | DNTD (208), SCTD (251) | 147 |
| MCM3 | 'Minichromosome maintenance protein 3', replication factor of the MCM complex, restricts replication to one round per cell cycle | Inactivated | Probably destruction of the MCM complex, prevention of replication | Unknown | 148 |
| PARG | Poly(ADP-ribose) glycohydrolase; removes poly(ADP-ribose) residues from proteins | Unknown | Cleavage does not alter enzymatic activity | DEID (256), MDVD (307) | 149 |
| PARP-1 | Poly(ADP-ribose) polymerase-1; involved in DNA repair and gene expression | Inactivated | Cleavage results in loss of catalytic activity and may prevent depletion of ATP which is required for apoptosis. | DEVD (214) | 24, 150–152 |
| PARP-2 | Poly(ADP-ribose) polymerase-2; involved in DNA repair | Inactivated | Cleavage between DNA binding and catalytic domain | LQMD (186) | 153 |
| Pol e | DNA polymerase epsilon (Pol e) catalytic subunit | Inactivated | Cleavage dissociates the N-terminal catalytic core from the C-terminus; can no longer bind PCNA or other Pol e subunits | DQLD (189), DMD (1185) | 154 |
| RAD21 | Component of the cohesin complex Human recombinase HsRad21 (homologous to RecA). Involved in homologous recombination and DNA repair | Inactivated | Cleavage products lack recombinase activity | DSPD (279) | 155 |
| RAD51 | Inactivated | | | DVLD (187) | 156 |
| RFC140 | Replication factor C (syn. DSB), DNA-dependent ATPase of the replication factor complex; involved in DNA replication and repair | Inactivated | Cleavage separates the DNA binding from its association domain and impairs DNA replication | DEVD (722) | 157–159 |
| Topo I | Topoisomerase I; breaks and rejoins DNA single strands | No effect? | Unconventional cleavage sites. Fragment still binds and cleaves DNA | PEDD (123), DEDD (146), EEED (170) | 160, 161 |
| Topo IIα | Topoisomerase IIα; X-ray repair, complementing defective, in Chinese hamster 4; involved in DNA double-strand break repair and V(DJ) recombination | Unknown | Inhibition of DNA repair | Unknown | 162 |
| XRCC4 | Unknown | | | Unknown | 163 |
### Table 1 (continued)

| Substrate | Physiological Function | Cleavage Effect | Consequences of Cleavage | Cleavage Sites<sup>a</sup> | References |
|-----------|-----------------------|-----------------|--------------------------|---------------------------|------------|
| **8. DNA-binding and transcription factors** | | | | | |
| AP-2z | Inducible transcription factor | Inactivated | Loss of DNA-binding activity | DRHD (19) | 164 |
| CREB | cAMP response element-binding protein | Inactivated | Antiapoptotic function is abolished | Putative site: ILND (140) or LSSOD (144) | 165 |
| c-Rel | NF-kB subunit | Inactivated | Loss of transcriptional activity | Unknown | 166 |
| GATA-1 | Yeast transcription factor used in two-hybrid assays | Inactivated | Cleavage results in loss of transcription in reporter gene assays | Unknown | 167 |
| HSF | Erythropoietic transcription factor | Inactivated | Loss of transcriptional activity results in impaired erythropoietin development | EGLD (42), EDLD (125), LSPD (144) | 168 |
| IκBα | Specialized isoform of basal transcription factor TFIID subunit | Inactivated | Elevated expression of hTAF(ii)80 triggers apoptosis | Unknown | 170 |
| LEDGF | Lens epithelium-derived growth factor, transcriptional coactivator | Inactivated | Cleavage abolishes survival function | EVPD (30), WEID (85), DAQD (486) | 172 |
| Max | Myc-associated factor | Inactivated | Cleavage by caspase-5 and -7 at an unusual glutamic acid residue | IEVE (10), SAFD (135) | 19 |
| MEF2A, C, D | Myocyte enhancer factor 2, isoforms A, C and D | Inactivated | Caspase cleavage generates a proapoptotic fragment with decreased transcriptional activity | MEF2A: SSYD (466), MEF2C: SSYD (422), MEF2D: LTED (288), DHLD (291) | 173, 174 |
| NF-κB p50 | Subunit of NF-κB | Inactivated | Loss of DNA binding | Unknown | 175 |
| NF-κB p65 | Subunit of NF-κB (RelA) | Inactivated | Cleavage generates a dominant-negative proapoptotic fragment | VFTD (465) | 175, 176 |
| NRF2 | Basic leucine-zipper transcription factor of the NF-E2 family; binds to antioxidant response elements | Inactivated | Overexpression of C-terminal fragment induces apoptosis; gene induction of detoxifying enzymes is abolished | TEVD (208), EELD (366) | 177 |
| PML-RARα | Fused oncogenic transcription factor in acute promyelocytic leukemia | Inactivated | Cleavage results in retargeting of PML to nuclear bodies | PHLD (523) | 178, 179 |
| RARα | Retinoid acid receptor-α | Inactivated | Loss of transcriptional activity | Unknown | 179 |
| Sp1 | Constitutive transcription factor | Inactivated | Loss of transcriptional activity | Unknown | 180 |
| SREBP-1/-2 | Sterol-regulatory element-binding protein-1/-2 involved in cholesterol metabolism | Activated | DNA-binding activity abolished | NSPD (590) | 181 |
| SRF | Serum response factor | Inactivated | Nonphysiological cleavage by caspases | SREBP-2: DEPD (468) | 182 |
| STAT1 | Signal transducer and activator of transcription-1 | Inactivated | Blockade of interferon and other cytokine signaling | MELD (694) | 184 |
| **9. RNA synthesis and splicing** | | | | | |
| BTF3 | Transcription initiation factor of RNA polymerase II | Unknown | Identified by 2D gel electrophoresis and *in vitro* cleavage | Putative site: QSVD (175) | 4 |
| hnRNPs (A0, A2/B1, A3, C1, C2, I, K, R) | Heterogeneous nuclear ribonucleoproteins involved in pre-mRNA-splicing and transport | Inactivated | Reduced RNA processing | hnRNP A1/A2: SYND (262), putative site, hnRNP A2/B1: KLD (49), VMRD (55), AEVD (76), putative sites, hnRNP C1, C2: NKTD (10), EGED (295), DDRD (298), GEDD (305), putative sites, hnRNP I: IVPD (7), LKTD (139), AAVD (172), hnRNP R: RAID (66) and DYYD (472) or KESD (87) and DYYD (472), putative sites | 2, 4, 185, 186 |
| KHSRP | KH-type splicing regulatory protein (syn. FUSE-binding protein 2), part of a complex that binds to an intronic splicing enhancer | Unknown | Identified by 2D gel electrophoresis and *in vitro* caspase-3 cleavage | Putative sites: IRKD (72), AFAD (76), IGGD (91), STPD (102), QLED (114), EDGD (116), SQGD (129) | 4 |
| NONO/ p54<sup>NN</sup> | Non-Pou domain-containing octamer-binding protein (syn. nuclear RNA-binding protein 54-kD, p54<sup>NN</sup>), splicing factor | Unknown | Identified by 2D gel electrophoresis and *in vitro* caspase-3 cleavage | Putative site: MIMP (421) | 4 |
Table 1 (continued)

| Substrate                          | Physiological Function                                                                 | Cleavage Effect | Consequences of Cleavage                                      | Cleavage Sitesa | References                                                                 |
|-----------------------------------|----------------------------------------------------------------------------------------|-----------------|--------------------------------------------------------------|-----------------|---------------------------------------------------------------------------|
| NS1-associated protein1           | RNA-binding protein that interacts with the nonstructural NS1 parvovirus protein        | Unknown         | Identified by 2D gel electrophoresis                        | Unknown         | 4                                                                         |
| Nucleolin                         | Abundant protein, involved in rRNA transcription, ribosome maturation and assembly     | Unknown         | Putative sites: TEID (455), and AMED (629) or GEID (633)    |                 | 2, 4                                                                      |
| RHA                               | RNA helicase A, mediates interactions between RNA polymerase II and transcription factors | Inactivated     | Cleavage results presumably in reduced transcription of particular genes | EEVD (167)      | 187, 188                                                                  |
| SFRS1                             | Member of the SR (serine- and arginine-rich) family of non-snRNP splicing factors, (syn. alternative splicing factor-2 or SRp30a) | Unknown         | Putative sites: DLKD (139), CYAD (151), VYRD (155), RKLD (176) |                 | 4                                                                         |
| SFRS9                             | Member of the SR (serine- and arginine-rich) family of non-snRNP splicing factors, involved in alternative splicing (syn. SRp30c) | Unknown         | Identified by 2D gel electrophoresis                        | Putative site: GWAD (6) | 4                                                                         |
| SRPK1                             | Serine/arginine splicing factor protein kinase 1                                        | Inactivated?    | Unknown                                                      | See Utz and Anderson189 |                                             |
| SRPK2                             | Serine/arginine splicing factor protein kinase 2                                        | Inactivated?    | Unknown                                                      | See Utz and Anderson189 |                                             |
| SS-B/La-autoantigen U1-70-kDa snRNP | Involved in RNA biogenesis; Sjogren's syndrome autoantigen                              | Inactivated     | Cleavage presumably results in disturbed Pol III transcription | DEHD (371) or DEHD (374) | 190                                                                      |
|                                  | Component of the U1 small nuclear ribonucleoprotein complex, involved in pre-mRNA-splicing |                 | Reduced RNA processing                                       | DGPD (341)      | 191–193                                                                   |
| 10. Protein translation           |                                                                                       |                 |                                                              |                 |                                                                           |
| 60S acidic ribosomal protein P0   | Component of the ribosome                                                             | Unknown         | Identified by 2D gel electrophoresis, not confirmed by in vitro cleavage | Putative sites: PRED (5), EESD (308), SDED (310) | 2, 4                                                                      |
| DAP5                              | Death-associated protein 5 (syn. p97, NAT1); member of the elf4G-family                | Activated       | Cleavage product stimulates translation from the IRES sites of c-Myc, Apaf-1, DAP5 and XIAP, supporting translation of apoptosis-related proteins | DETD (792)      | 17, 194                                                                   |
| eIF2α                             | Eukaryotic translation initiation factor 2α                                            | Inactivated?    | Generation of C-terminally truncated protein might result in protection of protein synthesis from PKR-mediated phosphorylation of eIF2α | AEVD (301) or DGDD (304) | 195, 196                                                                  |
| eIF3                              | p35 subunit of translation initiation factor eIF3                                       | Inactivated?    | Unknown                                                      | DLAD (242), DYED (256) | 197                                                                      |
| eIF4B                             | Eukaryotic translation initiation factor 4B                                            | Inactivated     | Generation of N-terminal truncated cleavage product, loss of poly(A)-binding and translation | DETD (45)       | 197, 198                                                                  |
| eIF4E-BP1                         | Eukaryotic translation initiation factor 4E-binding protein 1                          | Inactivated     | Fragment functions as a dominant-negative inhibitor of CAP-dependent translation | VLGD (25)       | 197, 199                                                                  |
| eIF4GI                            | Eukaryotic translation initiation factor 4GI, binds to the 5’ cap structure of mRNAs and facilitates binding of capped mRNA to 40S ribosomal subunits | Inactivated     | Inhibition of translation                                   | DLDL (492), DRLD (1136) | 200–202                                                                  |
| eIF4GII                           | Eukaryotic translation initiation factor 4GII, binds to the 5’ cap structure of mRNAs and facilitates binding of capped mRNA to 40S ribosomal subunits | Inactivated     | Shut-off of cap-dependent translation                        | Unknown         | 197, 203–205                                                             |
| NACα                              | Nascent polypeptide-associated complex α subunit of a complex that binds newly synthesized polypeptides and prevents them from incorrect translocation to the ER | Unknown         | Identified by 2D gel electrophoresis                        | Unknown         | 4                                                                         |
| PABP4                             | Poly(A)-binding protein 4 required for poly(A) shortening and translation initiation    | Unknown         | Identified by 2D gel electrophoresis                        | Unknown         | 4                                                                         |
| SRP72                             | 72-kDa signal recognition particle protein                                             | No effect?      | Cleaved SRP72 still transports signal peptide-containing proteins to the ER | SED (614)       | 206                                                                      |
| 11. Cytokines                     |                                                                                       |                 |                                                              |                 |                                                                           |
| pro-IL-1β                         | Interleukin-1β precursor                                                               | Activated       | Essential proinflammatory mediator                          | YVHD (116)      | 207–209                                                                   |
| pro-IL-16                         | Interleukin-16 precursor                                                               | Activated       | Induces T-cell chemotaxis                                   | SSTD (510)      | 210                                                                      |
Table 1 (continued)

| Substrate                  | Physiological Function                          | Cleavage Effect | Consequences of Cleavage                                                                 | Cleavage Sitesa | References |
|---------------------------|-------------------------------------------------|-----------------|------------------------------------------------------------------------------------------|-----------------|------------|
| pro-IL-18 IFN-g inducing factor | Endothelial monocyte-activating polypeptide-II  | Activated       | Induces IFN-g production Pro-EMAP-II is identical to the p43 component of the aminosyntypecomplex | LESD (36)       | 211–213    |
| pro-EMAP-II               | Ultra-associated polypeptide-II                | Activated       | Cleavage product is proapoptotic                                                          |                |            |
| Glutamate receptor        | Receptor family involved in neurotransmission  | Inactivated     | Cleavage of the glutamate receptor subunits GluR1, 2, 3, 4, 5, but not of NMDA receptor | Asp 865         | 219, 220   |
| RET                      | Tyrosine kinase receptor, proto-oncogene involved in Hirschsprung disease and multiple endocrine neoplasia type 2 | Inactivated     | RET induces apoptosis via its own cleavage by caspases through the liberation of a proapoptotic domain of RET | VSVD (707), DYLD (1017) | 221       |
| TCR-ζ                    | T-cell receptor zeta chain                      | Inactivated     | Cleavage of the cytoplasmic part results in loss of -ζ chain expression                   | GLLD (28) or YLLD (36), and DTYD (153) | 222       |
| TNF-R1                   | Tumor necrosis factor receptor-1 (p60)         | Inactivated     | Cleavage of the cytoplasmic tail at a nonconsensus motif by caspase-7                     | GELE (260)      | 223       |
| 13. Adapter proteins      |                                                 |                 |                                                                                          |                 |            |
| GrpL/Gads                 | Adapter of the Grb2 family in hematopoietic cells, couples to the T-cell receptor and SLP-76 to regulate transcription factors such as NF-AT | Inactivated     | Deletion of the C-terminal SH3 domain prevents recruitment of SLP-76 and leads to desensitization of antigen receptor signaling | DIND (235)      | 224, 225   |
| TRAF1                     | TNF-R-associated factor 1                       | Inactivated     | C-terminal cleavage product blocks NF-κB activation and promotes apoptosis                | LEVD (163)      | 226–228    |
| TRAF3                     | TNF-R-associated factor 3                       | Inactivated?    | Altered cellular distribution of the cleavage product                                      | EEAD (348), ESVD (368) | 229       |
| TXBP151                   | HLTLV-1 Tax-binding protein, antiapoptotic A20-binding protein | Inactivated     | Loss of antiapoptotic effect of TXBP15                                                  | Unknown         | 230       |
| 14. Tyr protein kinases    |                                                 |                 |                                                                                          |                 |            |
| ETK/BMX                   | Member of the Btk/Tec family of kinases         | Activated       | Overexpression of the fragment induces apoptosis                                          | ETK; DFPD (242) and a second unknown site EERD (19) | 231       |
| Fyn                       | T-cell Src kinase                               | Activated       | Removal of N-terminal myristoylation sites leads to reallocation and increased activity   | DIND (235)      | 224, 225   |
| Lyn                       | B-cell Src kinase                               | Activated       | Removal of N-terminal myristoylation sites leads to reallocation and increased activity   | DING (18)       | 233       |
| Sre                       | pp60(c-Src), proto-oncogene                     | Inactivated?    | Antiapoptotic effect is abolished                                                        | Unknown         | 234       |
| 15. Ser/Thr-Protein kinases in signal transduction | |                 |                                                                                          |                 |            |
| AKT                       | Important survival kinase (syn. PKB)           | Inactivated     | Loss of kinase activity and antiapoptotic function                                        | TVAD (108), EEMD (119), ECVD (482) | 235–238   |
| CaMK IIz                  | Calcium/calmodulin-dependent kinase IIz         | Inactivated?    | Effect on kinase activity not tested                                                       | Unknown         | 239       |
| CaMK IV                   | Calcium/calmodulin-dependent kinase IV          | Inactivated     | Cleavage within catalytic domain results in loss of activity                               | YWID (31), PAPD (176) | 239       |
| CaMKK                     | Calcium kinase                                  | Inactivated?    | Effect on kinase activity not tested                                                       | Unknown         | 239       |
| CaMKL                      | Calcium/calmodulin-dependent protein kinase     | Dysregulated    | C-terminal fragment retains kinase activity, while N-terminal fragment promotes apoptosis Proapoptotic cleavage converts an activator into an inhibitor of NF-κB, product fails to bind to Grb2 | Rat: DEND (62), (Human, mouse: putative DEND site at 369) DDVD (385) | 240, 241, 242 |
| HPK-1                     | Hematopoietic progenitor kinase-1, Ste20-related protein kinase | Dysregulated |                                                                                          |                 |            |
Table 1 (continued)

| Substrate | Physiological Function | Cleavage Effect | Consequences of Cleavage | Cleavage Sites | References |
|-----------|-----------------------|-----------------|--------------------------|----------------|------------|
| MASK      | Mst3 and SOK1-related kinase (MASK) of the germinal center kinase family | Activated | Proapoptotic, if overexpressed | DESD (305) | 243 |
| MEK       | MAP kinase kinase     | Inactivated     | Direct cleavage by caspases | Unknown | 244 |
| MEKK1     | MEK kinase-1; involved in stress signaling | Activated | Cleavage product is constitutively active, intracellularly redistributed and proapoptotic | Mouse: DTVD (874) (Human and rat: not conserved) | 245–247 |
| Mst1      | Mammalian STE20-related kinase-1 (Krs2); involved in stress signaling | Activated | Removal of C-terminal regulatory domain results in constitutive activity, relocalization and activation of stress kinases and caspases. | DEMD (326) | 248–250 |
| Mst2      | Mammalian STE20-related kinase (Krs1), involved in stress signaling | Activated | Cleavage results in a constitutively active kinase. Overexpression of the C-terminal kinase fragment induces apoptosis. | AETD (313) | 251 |
| PAK2      | P21-activated kinase 2 (syn. PAK66; PAK5) | Activated | Constitutive activation by separation of N-terminal regulatory and C-terminal catalytic domain, induces apoptotic morphology | SHVD (212) | 252, 253 |
| PKC δ     | Protein kinase C delta | Activated | Constitutively active kinase, proapoptotic | DMQD (329) | 254, 255 |
| PKC ε     | Protein kinase C epsilon | Activated | Constitutively active kinase | Human: SSPD (383), Mouse: SATD (383) | 256–258 |
| PKC η     | Protein kinase C eta  | Activated | Kinase-active fragment is proapoptotic | Unknown site in or upstream of the V3 region | 259 |
| PKC μ     | Protein kinase C mu   | Activated | Increased sensitivity to genotoxic stress | CQND (378) | 260, 261 |
| PKC θ     | Protein kinase C theta | Activated | C-terminal fragment is constitutively active and proapoptotic | DEVD (354) | 257, 262 |
| PKC γ     | Protein kinase C zeta | Activated | Constitutively active kinase, Caspase-dependent activation leads to eIF2-α phosphorylation and translation inhibition | EETD (210), DGVD (239), DLPD (251) | 256, 263, 264 |
| PRK1      | PKC-related kinase-1 (syn. PKN) | Activated | Constitutively active kinase | Unknown | 266 |
| PRK2      | PKC-related kinase-2   | Activated? | Proapoptotic; C-terminal fragment inhibits AKT and PDK-1 | DITD (117) | 5, 267 |
| Raf-1     | Ras-associated factor 1; important kinase in mitogenic signaling | Inactivated | Cleavage results in loss of Raf-1 antiapoptotic function | Unknown | 235 |
| RIP-1     | Receptor-interacting kinase-1, component of the TNF-R1 DISC | Inactivated | Proapoptotic cleavage by caspase-8 results in inhibition of NF-κB activation | LQLD (324) | 268, 269 |
| ROCK-1    | Rho-associated kinase-1 | Activated | Caspase-mediated activation results in activation of myosin light chain kinase and membrane blebbing | DETD (1113) | 270, 271 |
| SLK       | STE20-related kinase, JNK-pathway | Activated | Two cleavage products with distinct activities: N-terminal kinase promotes apoptosis and cytoskeletal rearrangement, the C-terminal fragment disassembles actin fibers | Mouse: DTQD (436) (site not conserved in human) | 272 |
| SPAK      | STE20/SPS1-related, proline alanine-rich kinase of STE20 kinase family | Unknown | | Rat: DEMD (398) | 273 |
| p70S6K    | p70 form of 56 kinase | Inactivated | Direct cleavage by caspases | Human: DEMD (392), Mouse: DEMD (402) | 274 |

16. Protein phosphatases

Calcineurin | Calmodulin-dependent phosphatase involved in NFAT activation and cytokine synthesis | Activated | Caspase-mediated constitutive activation triggers NF-AT activation and IL-2 release | DFGD (386) | 275, 276 |
| PP2A      | Protein phosphatase 2A | Activated | Caspases cleave regulatory subunit of PP2A and increase its activity | DEGD (218) | 277 |
Table 1 (continued)

| Substrate | Physiological Function | Cleavage Effect | Consequences of Cleavage | Cleavage Sites | References |
|-----------|------------------------|-----------------|--------------------------|----------------|------------|
| FTase     | Farnesyltransferase, attaches farnesyl groups to cysteine residues of proteins | Inactivated | Cleavage of α-subunit (common to FTase and GTTase), expression of cleavage product induces cell death | VSLD (59) | 278 |
| GGTase I | Geranylgeranylttransferase I, attaches geranylgeranyl groups to cysteine residues | Inactivated | Cleavage of α-subunit (common to FTase and GTTase), expression of cleavage product induces cell death | VSLD (59) | 278 |
| O-GlcNAase | β-O-linked-N-acetylglucosaminidase; releases O-GlcNAc residues from peptides | No effect | Cleavage has no effect on enzyme activity in vitro | Unknown | 279 |
| rTG | Tissue transglutaminase (TG-2) crosslinks proteins and assembles scaffolds that prevent leakage of intracellular components | Inactivated | Cleaved late in apoptosis, results in loss of crosslinking activity | Unknown | 280 |

18. Protein degradation

- Calpastatin: Calpain inhibitor, Cleavage Effect: Inactivated, Consequences of Cleavage: Decreased inhibition of calpain, References: ALDD (137), LSSD (203), ALAD (404), 281, 282
- Cbl: Adapter protein with ubiquitin ligase activity, negative regulator of T-cell activation, downregulates receptor tyrosine kinases by ubiquitinylation, Cleavage Effect: Unknown, References: 235
- Cbl-b: Cbl-related protein with ubiquitin ligase activity, downregulates receptor tyrosine kinase and PI3K signaling, Cleavage Effect: Unknown, References: 235
- Nedd4: 'Neural-expressed developmentally downregulated gene 4 protein', ubiquitin protein ligase, Cleavage Effect: Unknown, Consequences of Cleavage: Cleavage products do not affect apoptosis, enzyme activity of NEDD4 presumably not impaired, References: DQPD (206), 283
- PA28γ: Proteasome activator 28 γ-subunit, Cleavage Effect: Unknown, References: 284
- PAI-2: Plasminogen activator inhibitor type 2, Cleavage Effect: Unknown, Consequences of Cleavage: Function as putative cytoprotective protease inhibitor may be abolished, References: 285
- UFD2: Ubiquitin fusion degradation protein-2, with E3 ligase activity, Cleavage Effect: Inactivated, Consequences of Cleavage: E3 activity is abolished in vitro, References: MDID (109), VDVD (123), 286

19. G protein signaling

- Cdc42: Ras-related GTP-binding protein, provides survival signals and controls cytoskeletal architecture, Cleavage Effect: Inactivated, Consequences of Cleavage: Antia apoptotic function abolished. Mutation of the cleavage site of Cdc42 provides protection, References: DLRD (121), 287
- D4-GDI: D4-GDP dissociation inhibitor (syn. Rho-GDI 2; Ly-GDI), inhibitor of Rho GTPases, Cleavage Effect: Inactivated, Consequences of Cleavage: Cleavage product translocates to the nucleus, defective Rho GTPase signaling, References: DELD (19), 288, 289
- Rabaptin-5: Small GTPase, rate-limiting component in membrane fusion in the early endocytic pathway, Cleavage Effect: Inactivated, Consequences of Cleavage: Cleavage blocks endosome fusion, References: DESD (438), 290
- Rac: Ras-related GTP-binding protein, Cleavage Effect: Inactivated?, Consequences of Cleavage: May be involved in alterations of nuclear pore transport. Cleavage not confirmed in vitro, References: DLRD (121), 287
- Ran-GAP: Ran GTPase activating protein 1, involved in nuclear transport, Cleavage Effect: Inactivated?, References: 291
- Ras-GAP: Ras GTPase-activating protein, Cleavage Effect: Activated, inactivated, Consequences of Cleavage: Cleavage results in nuclear export, References: DEGD (157), DTVD (459), 235, 292, 293
- TIAM1: Rac-specific guanine nucleotide exchange factor, Cleavage Effect: Inactivated, Consequences of Cleavage: Functional inactivation, cannot stimulate GDP loading of Rac Fails to induce IL-2 transcription; diminished capacity to activate AP-1, NF-κB, NF-AT; can still activate JNK; but not p38, References: DETD (993), 294
- Vav-1: Hematopoietic proto-oncogene, guanine nucleotide exchange factor, Cleavage Effect: Inactivated, References: DQID (150), DLYD (161), 295

20. Calcium, c-AMP, c-GMP and Lipid metabolism

- CCT-ε: CTP : phosphocholine cytidylyltransferase ε, involved in phosphatidyl choline synthesis, Cleavage Effect: Activated, Consequences of Cleavage: Cleavage results in nuclear export, References: TEED (28), 296
Table 1 (continued)

| Substrate | Physiological Function | Cleavage Effect | Consequences of Cleavage | Cleavage Sites | References |
|-----------|------------------------|-----------------|--------------------------|----------------|------------|
| IP(3)R-1/-2 | Inositol 1,4,5-triphosphate receptor-1 and -2 | Inactivated | Decrease in IP(3)-gated Ca\(^{2+}\) channel activity | Mouse IP(3)R-1: DEVD (1892) | 297–299 |
| PIP5K-I | Phosphatidylinositol 5-kinase-1, synthesizes phosphatidyl-inositol 4,5-bisphosphate which inhibits caspases | Inactivated | Inactivation contributes to progression of apoptosis | DIPD (279) | 300 |
| PDE4A5 | cAMP-specific phosphodiesterase 4A5 | Dysregulated | Cleavage removes SH3-binding domain and results in altered intracellular targeting and Lyn kinase interaction | Mouse: DAVID (72) | 301 |
| PDE5A1 | cGMP-binding phosphodiesterase 5A1 | Inactivated? | | Unknown | 302 |
| PDE6 | cGMP-binding phosphodiesterase 6 | Inactivated? | Reduced cGMP-hydrolyzing activity | Putative site: DFVD (167) | 302 |
| PDE10A2 | Cytosolic phospholipase A2 | Cleaved | Cleavage blocks PLA2 activity and prevents production of lipid mediators; may have immunosuppressive function | VEVD (770) | 318 |
| PMCA-2 | Neuron-specific plasma membrane Ca\(^{2+}\)ATPase isoform 2 | Cleaved | Cleavage abolishes interaction with i-cat and disables antiapoptotic function | VEVD (329) | 317–319 |
| PMCA-4 | Ubiquitous plasma membrane Ca\(^{2+}\)ATPase isoform 4 | Cleaved | Phosphorylated PLC is resistant against cleavage, Cleavage facilitates apoptosis | DSSD (64) | 314 |
| iPLA(2) | Calcium-independent phospholipase A2 | Activated | Fragment accelerates phospholipid turnover and contributes to apoptotic membrane changes | DSSD (64) | 314 |
| cPLA(2) | Cytosolic phospholipase A2 \(A_2\) (type IVA), involved in arachidonic acid metabolism | Cleaved | | AEPD (770) | 307 |
| PLC-\(\gamma\)-1 | Phospholipase C-\(\gamma\)-1, involved in mitogenic signaling | Cleaved | | DEID (180) | 28, 303 |

21. Neurodegeneration

| Substrate | Physiological Function | Cleavage Effect | Consequences of Cleavage | Cleavage Sites | References |
|-----------|------------------------|-----------------|--------------------------|----------------|------------|
| Androgen receptor | Polyglutamine tract protein, defective in spinal bulb muscular atrophy (Kennedy’s disease) | Aggregates | Aggregation of the truncated protein may result in neurodegeneration | DEED (155) | 308, 309 |
| APLP1 | Amyloid precursor protein-like protein -1, related to APP | Aggregates? | Cleavage generates a cytotoxic C-terminal fragment similar to C31 in APP | VEVD (620) | 310 |
| APP | \(\beta\)-Amyloid precursor protein, involved in Alzheimer’s disease | Aggregates | Cleavage results in generation of the proapoptotic C-terminal C31-peptide | VEVD (739) | 31, 311 |
| Ataxin-3 | Polyglutamine tract protein, defective in spinocerebellar ataxia type 3 | Aggregates | Aggregation of the truncated protein may result in neurodegeneration | Putative sites: LISD (145), DLFD (171), LDED (225), DSSD (228), DLYD (109) | 308, 312, 313 |
| Atrophin-1 | Polyglutamine tract protein, defective in Dentatorubral pallidolysian atrophy (syn. DRPLA protein) | Aggregates | Cleavage abolishes interaction with i-cat and disables antiapoptotic function | AQRD (345) | 317, 318 |
| Calsenilin | Member of the recoverin family of calcium-binding proteins, interacts with presenilins | Inactivated | May be involved in Alzheimer’s disease | DSSD (64) | 314 |
| Huntingtin | Polyglutamine tract protein, defective in Huntington’s disease | Cleaved | N-terminal fragment is cytotoxic and triggers caspase activation | DSVD (513), DEED (530), IVDL (586) | 30, 315 |
| Parkin | Polyglutamine tract protein, defective in Parkinson’s disease | Cleaved | Protein degradation abolishes antiapoptotic function | LHTD (126) | 316 |
| Presenilin-1 | Involved in Alzheimer’s disease | Cleaved | Cleavage abolishes interaction with i-cat and disables antiapoptotic function | AQRD (345) | 317, 318 |
| Presenilin-2 | Involved in Alzheimer’s disease | Cleaved | Cleavage abolishes interaction with i-cat and disables antiapoptotic function | DSSD (64) | 314 |

22. Viral proteins

| Substrate | Physiological Function | Cleavage Effect | Consequences of Cleavage | Cleavage Sites | References |
|-----------|------------------------|-----------------|--------------------------|----------------|------------|
| Bcl-2 homologs | Viral Bcl-2-homolog encoded by \(\gamma\)-Herpesvirus 68 | No effect | Unlike mammalian Bcl-2, most viral Bcl-2 proteins are not cleaved; \(\gamma\)-HSV68 Bcl-2 is cleaved, but not converted to a proapoptotic form | DCVD (31) | 50 |
| CrmA | Cytokine response modifier A, serpin-like caspase inhibitor of poxvirus | Activated | Unlike IAPs, CrmA requires peptide bond hydrolysis for caspase-inhibitory action | LVAD (303) | 320 |
The search for caspase substrates has brought several major questions into focus. For instance, is there a critical death substrate or what is the minimal set of proteins that must be cleaved in order to induce the phenotypic hallmarks of apoptosis? How is caspase substrate cleavage coordinated with other cellular processes, such as removal of dead cells, or presumably unrelated events including cell proliferation and differentiation? Although the significance of cleavage is not well understood for many substrates, the intense study of caspase substrates has recently shed some light on these questions. Here, we discuss several topics that have emerged from the accumulating knowledge regarding the role of caspase substrates in different biological processes.

Key morphological alterations are determined by caspase substrate cleavage

For most proteins, the consequences of their cleavage are poorly understood. In a few cases, however, proteolysis of certain components can be linked to discrete morphological changes of cell death. A classical example is the DNase inhibitor ICAD. Cleavage of ICAD by caspase-3 liberates the active CAD nuclease that mediates apoptotic DNA fragmentation (for references, see Table 1). In addition, the cleavage of acinus and helicard, a DNA helicase, contributes to chromatin condensation and nuclear remodeling. The cleavage of several other substrates, including gelsolin as well as the kinases ROCK-1 and PAK2, has been implicated in membrane blebbing, a classical morphological feature. Gelsolin is cleaved by caspase-3 to generate a constitutively active CAD nuclease that mediates apoptotic DNA fragmentation. Whereas cell death often results in membrane blebbing, a classical morphological feature, Gelsolin is cleaved by caspase-3 to generate a constitutively active fragment that can depolymerize F-actin. Gelsolin-deficient neutrophils exhibit greatly delayed membrane blebbing during apoptosis, implying that membrane blebbing requires actin reorganization mediated by caspase-activated gelsolin. Caspases also cleave and thereby activate ROCK-1 leading to the phosphorylation of myosin light chains, which finally results in membrane blebbing.

| Substrate | Physiological Function | Cleavage Effect | Consequences of Cleavage | Cleavage Sites* | References |
|-----------|-----------------------|----------------|--------------------------|-----------------|------------|
| M2 (influenza A) | Virus-specific ion channel membrane protein of influenza A virus nucleocapsid protein of influenza A and B viruses | Unknown | Cleavage may attenuate virus production | DVDD (88) | 321 |
| NP (influenza A and B) | Nonstructural protein 5A of hepatitis C virus | Unknown | Cleavage may attenuate virus production | Influenza A: METD (16), Influenza B: MDID (7), SEAD (61) | 321, 322 |
| NS5A (HCV) | Transmissible gastroenteritis coronavirus (TGEV) nucleocapsid protein | Unknown | N-terminal deleted protein translocates to the nucleus and has transactuating function | Putative sites: TEVD (154), SGVD (396) | 323, 324 |
| Nucleoporin (TGEV) | Transmissible gastroenteritis coronavirus (TGEV) nucleocapsid protein | Unknown | Cleavage may limit virus production | VVPD (359) | 325 |
| p35 | Pancaspase inhibitor of baculovirus | Activated | Cleavage is required for caspase inhibition by p35 | DQMD (87) | 326, 327 |
| 23. Other substrates | | | | | |
| AHNAK | Autoantigen in systemic lupus erythematosus. DNA-binding phosphoprotein | Unknown | Unknown | Unknown | 328 |
| CPSII | Carboxymethyl phosphatase synthetase II, required for pyrimidine nucleotide synthesis | Inactivated | EAVD (1371) in catalytic B2 domain and VACD (1143) in allosteric B3 domain | 329 |
| F1A | Mammalian homolog of FEM-1 (syn. FEM1/1), ankyrin repeat-containing protein | Activated? | F1A is proapoptotic and binds to death receptors in 2-hybrid assays. Loses apoptosis-inducing ability upon cleavage | DNID (342) | 330 |
| FEM-1 | Involved in sex-specific cell elimination in C. elegans, necessary for male phenotype | Activated? | Caspase cleavage promotes apoptosis-inducing property of FEM-1, which interacts with Ced-4 | ELLD (320) | 331 |
| FKBP46 | FK506 binding protein 46, insect nuclear immunophilin | Unknown | Unknown | Unknown | 332 |
| GCL | Glutamate-cysteine ligase, rate-limiting enzyme in glutathione synthesis | Inactivated | Cleavage of the catalytic subunit results in loss of the antioxidant glutathione | AVVD (499) | 333 |
| Hsp90 | Product of the putative set oncogene | Unknown | Cleavage confirmed by in vitro caspase-3 cleavage | DEED (259) | 96 |
| PDC-E2 | Pyruvate dehydrogenase complex E2, autoantigen | Unknown | SNHD (18) | 335 |

*If not otherwise indicated, the cleavage sites refer to the human sequence.

**During typesetting of this manuscript additional caspase substrates have been identified including the large subunit of RNA polymerase II, the vesicle-tethering Golgi protein p. 115, the neuronal Ras guanine nucleotide exchange factor GRASP-1, the hematopoietic transcription factor FL1-1, SRPK1 and SRPK2, two kinases of the serine/arginine splicing factors, the K10 retroviral polyprotein HERV-K10 gag, adenovirus early region 1A proteins, and baculovirus apoptotic suppressor protein p 49.
two proteins involved in filament organization. These cleavages may directly contribute to apoptotic changes in cell shape. Caspases attack targets of the cortical actin network such as fodrin, and several components of the focal adhesion complex which links cortical actin filaments and membrane proteins to the extracellular matrix. Examples of this kind of substrates are focal adhesion kinase, Cas or paxillin. Cleavage of these proteins presumably contributes to cell shrinkage and cell detachment and, importantly, will interrupt antiapoptotic integrin signaling. A large percentage of caspase substrates are involved in cell adhesion or mediate cell–cell communication in adherens and gap junctions, or in desmosomes. Examples are β-catenin, E-cadherin, plakoglobin or desmoglein.

In the course of apoptosis, disruption of the endoplasmic reticulum and Golgi apparatus also takes place. Cleavage of golgin-160 and GRASP65 was suggested to cause disassembly of the Golgi complex, and proteolysis of Bap31 disrupts the transport between the ER and the Golgi complex. During apoptosis, vesicle transport processes are also impaired, for instance by the cleavage of rabaptin-5 or kinectin.

Caspases initiate the destruction of the nucleus where a huge variety of different proteins are cleaved. By 2D gel electrophoresis it has been recently determined that approximately 70 nuclear matrix proteins are consistently degraded or translocated during apoptosis, irrespective of the cell type or apoptotic stimulus. Many cleavages lead to nuclear lamina disassembly, and the cleavage of several components of the nuclear pore results in impaired nuclear transport. Inhibition of DNA repair, for instance by the cleavage of PARP-1 or the kinases ATM and DNA-PK, has been long thought to promote the apoptosis process. Other targeted factors are involved in DNA synthesis and replication, such as DNA polymerase Pol e, MCM3 or replication factor RFC140. In addition, various proteins that bind to chromatin, and either fulfill a transcriptional role or have structural functions in the nuclear matrix, are destroyed. In almost all cases, these cleavages result in the generation of proteins that are no longer able to bind to DNA or to stabilize chromatin in the nuclear matrix. With a few exceptions that are discussed below, virtually all pathways of macromolecular synthesis are impaired by caspases. Cleavage of RNA helicase A and multiple splicing factors, including U1 70-kDa snRNP and at least eight different heterogeneous nuclear ribonucleoproteins (hnRNPs), leads to a general shut-off of RNA synthesis, processing and transport. Moreover, protein synthesis is blocked either by the inactivation of translation initiation factors, including eIF2α, eIF3 and eIF4G proteins, or by the activation of PKR kinase that blocks protein synthesis through eIF2-α phosphorylation.

**Caspase substrates in signal transduction**

A tremendous variety of proteins involved in signal transduction are cleaved by caspases. The proteolytic cleavage can either lead to the functional inhibition or to the activation of these mediators. In some cases, it has been established that caspase-mediated activation of these molecules is involved in transduction and amplification of the apoptotic signal. Caspases turn off cell-protective mechanisms and activate pathways that lead to cell destruction. Classical apoptosis inhibitors that are cleaved by caspases are Bcl-2 proteins or the caspase-8 inhibitor c-FLIP. The cleavage of Bcl-2 and Bcl-xL resulting in the removal of the N-terminal BH4 domain not only leads to a loss of their antiapoptotic function, but even converts them to proapoptotic proteins. Similarly, during death receptor-mediated apoptosis caspase-8 cleaves the Bcl-2 member Bid generating an active C-terminal fragment that induces the proapoptotic release of cytochrome c from mitochondria. The conversion of antiapoptotic into proapoptotic regulators constitutes a positive feedback loop in the terminal phase of apoptosis, removing apoptotic inhibitors and promoting caspase activation. It is interesting to note that certain viral Bcl-2 proteins can also be cleaved by caspases, but in these cases no proapoptotic fragments are generated.

Several kinases and transcription factors with antiapoptotic activity are inactivated during apoptosis. Akt and Raf-1 provide two examples of antiapoptotic kinases that are cleaved by caspase-3. As both kinases can inactivate proapoptotic molecules such as Bad, their degradation presumably constitutes a positive feedback loop in apoptosis. Antiapoptotic transcription factors inhibited by caspases include the cAMP-responsive factor CREB, heat-shock factor HSF-1 and NF-κB. The NF-κB pathway is a paradigm of how caspase cleavage may result in a complete loss of the transcription factor’s antiapoptotic function: (i) Cleavage of NF-κB subunit p65 (RelA) generates a dominant-negative fragment that is still able to bind to DNA but looses its transactivating activity, and therefore functions as a dominant-negative inhibitor. (ii) The NF-κB inhibitor IκB-α is normally inducibly degraded by the proteasome. The N-terminal cleavage of IκB-α by caspases generates a constitutive super-repressor that can no longer be removed by the proteasome. (iii) The cleavage of the adapter proteins TRAF-1 and RIP-1 that are involved in receptor-mediated pathways also contributes to impaired NF-κB activation and antiapoptotic capacity. Thus, cells have elaborate mechanisms in order to interrupt antiapoptotic signaling efficiently.

While some substrates are functionally inactivated upon caspase-mediated cleavage, other proteins and enzymes can be activated, mostly by removing an inhibitory or regulatory domain within the caspase target. The physiological consequence of this gain-of-function cleavage for apoptosis remains mostly unclear. Several members of the PKC family and MAP kinase pathway are constitutively activated by the separation of an N-terminal regulatory and the C-terminal catalytic domain. Examples are the p21-activated kinase PAK2 as well as ROCK-1. As described above, activation of PAK2 and ROCK-1 is important for cytoskeletal reorganization and plasma membrane blebbing. In the case of MEKK1, expression of the caspase-cleaved kinase fragment induces caspase activation, thereby providing a positive feedback loop for apoptosis. Epithelial cells undergo apoptosis if they are detached from the basement membrane, a process called anoikis. MEKK1 is activated following cell detachment, and blockade of either MEKK1 or caspase activity blocks anoikis. Cleavage of several MST kinases by caspase-3 also yields...
constitutively active molecules and potent inducers of apoptosis. Apoptosis induction by all these upstream kinases in the SAPK/JNK pathway may be explained in part by their ability to activate JNK, which then phosphorylates and inactivates Bcl-2.

Most kinase pathways exert antiapoptotic functions. It is thus not unexpected that a major cellular protein phosphatase, PP2A, which counteracts the survival function of kinases, is activated by caspases. Protein phosphorylation can also protect caspase substrates from proteolysis. This has been convincingly demonstrated for Bid that is protected from caspase-8 cleavage through phosphorylation by casein kinases I and II. Another example is Max, a transcription factor in the c-Myc network, which can be cleaved only if dephosphorylated. A very intriguing finding has been recently made for C/EBPβ. The transcription factor itself is not cleaved by caspases, but curiously acts as caspase inhibitor upon phosphorylation. Threonine phosphorylation of C/EBPβ within a KTVD sequence creates a noncleavable mimic of an XEXD cleavage site, which binds caspases and thereby inhibits caspase action. Hence, such dummies of caspase substrates may represent a novel survival mechanism.

Some peculiarities of substrate cleavage

Caspase cleavage can also result in the cellular redistribution and dislocation of signaling mediators. In some cases, such as the Grb2 adapter protein GrpL or the phosphodiesterase PDE4A5, an SH3-domain within the substrate is removed causing its inability to bind to physiological interaction partners. A change of subcellular localization following caspase cleavage has also been observed for the kinases Fyn and MEKK1. Another notable example is Bid. Upon cleavage by caspase-8, the proapoptotic p15 fragment of Bid undergoes post-translational rather than the classical cotranslational N-myristoylation at a glycine residue that becomes newly exposed by the cleavage. This postproteolytic N-myristoylation then enables Bid to target mitochondria and serves as an activating switch, which strongly enhances cytochrome c release.

Apoptosis is generally associated with a shut-down of cap-dependent protein translation, which is mediated by caspase cleavage of several translation factors. Interestingly, it has been recently observed that during apoptosis, translation of a subset of mRNAs prevails. The reason for this is presumably a switch from cap-dependent to internal ribosome entry site (IRES)-mediated protein translation. DAP-5, a member of the elf4G family, is activated by caspases and stimulates translation from the IRES sites of c-Myc, Apaf-1, and its own mRNA. Thus, DAP-5 is a rather unique caspase-activated factor that supports cap-independent translation of apoptosis-related proteins and thereby may amplify the apoptosis cascade.

Most caspase substrates identified so far are cleaved by caspase-3. This has been convincingly shown in the system of MCF-7 breast carcinoma cells that lack caspase-3, and caspase-3 re-expressing derivatives. Nevertheless, several substrates that are efficiently cleaved by caspase-3 can also be targeted by caspase-7, suggesting an at least partial redundancy of both caspases. Caspase-7 activity is upregulated in cells of caspase-3-deficient mice, where it might compensate for the loss of caspase-3. Caspase-7 and -5, but not caspase-3, cleave transcription factor Max. Interestingly, in this case Max is not cleaved at the classical aspartate residue in the P1 position, but at an unusual glutamate residue. Cleavage of the cytosplasmic tail of TNF-R1, the cardiac myosin light chain vMLC and connexin 45.6 at a glutamate instead of an aspartate residue are further examples. Cleavage at these noncanonical sites suggests that the specificity of caspases may in fact be broader than generally thought. Also, the Drosophila caspase DRONC can cleave substrates following glutamate residues. Caspase-7 not only cleaves substrates at atypical motifs, but can be activated itself by a rather unusual processing event. It has been reported that various serine proteases can trigger the proteolytic activity of the caspase-7 zymogen. For instance, cathepsin G activates caspase-7 by cleaving at a glutamate bond, indicating that the cleavage specificity at aspartic acid is not strictly required for caspase activation.

The interaction of caspases with other classes of proteases, including calpains, cathepsins or the proteasome, is poorly understood. When searching for caspase substrates, it must be considered that high concentrations of caspase inhibitors, such as the fluoromethylketone zVAD-fmk, are less specific than often anticipated, because calpains are inhibited as well. Several substrates of caspases are also cleaved by calpains including structural proteins, such as fodrin, keratins and β-actin, and proteins involved in signal transduction, such as Bid, Bax, focal adhesion kinase and many others. It has been found that caspases and calpains interfere with each other, resulting in mutual protease activation. Caspases can indirectly activate calpain by cleavage and inactivation of its inhibitor calpastatin, and thereby turn on downstream events leading to cellular destruction. However, it is still controversial as to whether calpains function upstream or downstream of caspases. It has also been reported that calpains cleave procaspases to generate proteolytically inactive caspase fragments.

Caspases are not only involved in apoptosis but also in the induction of inflammation. In fact, the former notion that apoptosis and inflammation are exclusive processes should be replaced, as both processes are linked at various levels. Caspase-1 processes and maturates the cytokine precursors pro-IL-1β and pro-IL-18, also known as IFN-γ-inducing factor. Although caspase-1 is required mainly for induction of inflammation, it can process the effector caspases-3, -6 and -7 and may initiate apoptosis under certain conditions. Effector caspases can also activate pro-IL-16 and pro-EMAP-II, an endothelial-monocyte-activating polypeptide. This precursor of EMAP-II is an intriguing substrate, because it exerts a dual function: Pro-EMAP-II is identical to the p43 cofactor of the aminoacyl-tRNA synthetase complex. After cleavage, preferentially by caspase-7, its t-RNA binding capacity is lost and protein translation is blocked. The translation arrest is accompanied by the release of the EMAP-II cytokine that may play a role in the engulfment of apoptotic cells by phagocytes. Caspase-mediated substrate cleavage therefore has multiple effects summarized as (i) a halt of cell cycle progression, (ii) disabling of repair
mechanisms, (iii) disassembly of molecular structures, (iv) cell detachment, and (v) maturation of cytokine precursors.

Substrate cleavage at the balance between necrosis and apoptosis

Although caspases are presumably not essential for necrotic cell death, recent evidence suggests that the cleavage of certain substrates may determine the form of cell death. One of the first death substrates found to be cleaved by caspases was PARP-1, which catalyzes the transfer of ADP-ribose polymers to nuclear proteins and thus presumably facilitates DNA repair.24 Owing to its role in DNA repair, it was originally hypothesized that the cleavage of PARP may lead to lethal DNA damage and compromise most of its DNA repair activity, and thus may contribute to the demise of the cell. However, PARP(C0/C0) 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.25 Thus, cleavage of PARP may be a characteristic event, but is presumably dispensable for most apoptotic pathways.

New evidence, however, suggests that PARP inactivation by caspase-3 is important for turning off an energetically expensive DNA repair pathway and for maintaining ATP levels that are required for the execution of apoptosis. PARP is rapidly activated during oxidative stress and DNA damage. Activated PARP then transfers more than 100 ADP-ribose moieties to each acceptor site in target proteins, and each cycle of ADP-ribosylation is coupled with consumption of one NAD molecule, which is metabolically equivalent to four ATP molecules. Hence, it can be imagined that excessive activation of PARP will quickly deplete cellular energy stores. In the absence of an energy pool sufficient to execute apoptosis or to maintain ionic homeostasis, cells can die quickly by necrosis. Indeed, when cells engineered to express caspase-resistant PARP are treated with apoptotic stimuli, they undergo extensive necrosis instead of apoptosis.26 Consistent with the requirement of maintaining cellular energy during apoptosis, cells artificially depleted of ATP undergo necrosis instead of apoptosis under conditions that would normally trigger caspase activation.27 Thus, cleavage of PARP prevents depletion of the cellular energy needed for apoptosis and thus may function as a molecular switch between apoptotic and necrotic cell death. Similar to PARP, also the cleavage of other substrates may provide a link between apoptosis and necrosis. For instance, cleavage and inactivation of the plasma membrane calcium ATPase PMCA-4, which removes calcium from the cytosol, disturbs ion homeostasis.28 The subsequent cellular calcium overload may be responsible for the secondary necrosis that is observed in the late stages of apoptosis.

Role of caspase substrates in disease progression

Increased caspase activation has been recently demonstrated in various diseases. However, the cleavage of several substrates may not only contribute to increased tissue damage, but may also play an active role in disease progression. Such a direct role of substrate cleavage has been most intensively studied in neurodegeneration and autoimmune diseases. Autoimmunity to intracellular proteins has been identified as an important factor in autoimmune diseases. Massive apoptosis or defective clearance may lead to an accumulation of apoptotic cells that concentrate caspase-cleaved proteins in their apoptotic bodies and membrane blebs. The presence of autoantibodies against caspase substrates, such as lamins, fodrin, DNA-PK, PARP or NuMA, has been demonstrated in several autoimmune diseases.29 Cleavage of these autoantigens presumably enhances their immunogenicity by exposing cryptic neoepitopes. The cleaved proteins are then processed and presented by dendritic cells to circulating autoreactive T cells, triggering an autoimmune response.

The cleavage of specific substrates can be directly linked to the pathogenesis of certain neurodegenerative disorders. 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. Huntington is cleaved by caspase-3 and results in an N-terminal fragment, which aggregates and forms nuclear inclusions that are directly cytotoxic for neurons.30 Huntington’s disease manifests only if huntingtin exceeds 35 glutamine residues. Because the rate of caspase cleavage of huntingtin correlates with the length of the polyglutamine stretch, accumulation of the fragment may cause a vicious cycle. A pathogenic role of caspase cleavage has also been implicated in other neurodegenerative disorders. Similar to huntingtin, the polyglutamine tract proteins atrophin-1, androgen receptor and ataxin-3 are caspase substrates. Indeed, mutations of the caspase recognition sites at atrophin-1 and androgen receptor abrogate their cytotoxicity in vitro.

Alzheimer’s disease is characterized by brain lesions of neurofibrillary tangles, and senile plaques built of aggregates of the β-amyloid peptide. Aggregates of β-amyloid peptide induce neuronal apoptosis, and increased production of β-amyloid peptide has been postulated as an important pathologic mechanism in early-onset familial Alzheimer’s disease. Effector caspases presumably increase β-amyloid production by several mechanisms. Loss-of-function mutations in the presenilin-1 and -2 genes are responsible for the majority of familial Alzheimer’s disease and are thought to increase β-amyloid production. Caspase-3 can cleave and inactivate presenilins, which may mimic the effect of pathologic presenilin mutations. The 40- to 42-amino-acid β-amyloid peptide is derived from proteolytic processing of the amyloid precursor protein (APP) at two sites by the β- and γ-secretase. Caspase-3 cleaves APP at a site different from the γ-secretase site.31 Nevertheless, the N-terminal caspase cleavage product of APP strongly facilitates the production of β-amyloid peptide, and appears itself to be a component of senile plaques found in Alzheimer patients. Because caspase-3 activation and APP cleavage are also induced in vitro after ischemic brain injury, a risk factor for Alzheimer’s disease, these results provide another example of a positive feedback loop between caspase substrate cleavage and neurodegeneration. Neuronal apoptosis from ischemia or other causes activates caspase-3 and stimulates APP
cleavage, which increases the propensity for β-amloid peptide production. In turn, increased extracellular β-amloid peptide production may induce neuronal apoptosis, leading to further deposition of senile plaques. The cytotoxic properties of their cleavage products illustrate that specific caspase substrates are not only involved in cell destruction, but also fulfill an active role in the exacerbation of disease processes.

Caspases: more than just killers?
A strikingly large number of caspase targets are involved in cell cycle regulation. This has led to speculations that caspases are not only involved in cell death but also in proliferative events. Supportive, yet indirect evidence for a role of caspases in cell growth is the observation that proliferation of primary T cells is inhibited by cell-permeable caspase inhibitors. Moreover, interference with pathways leading to caspase processing, as in FADD-deficient or Bcl-2-transgenic mice, also results in impaired mature T-cell proliferation.

Several negative regulators including Wee1, an inhibitor of the cell cycle-regulatory kinases CDK2 and CDC2, as well as CDC27, a component of the anaphase-promoting complex, are cleaved by caspases. Wee1 is a critical component of the G2/M cell cycle checkpoint machinery and mediates cell cycle arrest by phosphorylation of CDC2. Therefore, cleavage of Wee1 in proliferating lymphocytes could lead to its inactivation, thus allowing cell cycle progression. Of note, Wee1 processing by caspases during apoptosis in Jurkat T cells correlated with a strong decrease in Wee1 activity and an increase in CDC2 activity. Moreover, the cyclin inhibitors p21Waf1 and p27Kip1 are targeted by caspases resulting in increased CDK2 activity that could allow cell cycle progression.

If caspases are activated during mitosis, a critical question is then, how could caspase cleavage be restricted to those cell cycle regulators, while leaving other vital proteins intact? The answer could lie in a specific subcellular compartmentalization of caspases, the existence of scaffold proteins or a different accessibility of cleavable substrates. Some caspases are translocated to a certain organelle during activation, and in some cell types certain caspases have been localized in the nucleus. Interestingly, it has been found that, although caspases were activated and Wee1 was cleaved after mitogenic T-cell stimulation, neither DNA replication factor RFC140 nor ICAD were cleaved in proliferating T cells. Cleavage of RFC140 and ICAD would lead to inhibition of DNA replication and fragmentation of genomic DNA, events that are not compatible with cell proliferation. Thus, selective substrate processing could explain why nonapoptotic cells survive and proliferate despite caspases being activated.

Certainly, there exist many links, also at the morphological level, between the processes of cell death and proliferation. However, it must be emphasized that the view of a potential involvement of caspases in proliferation is largely based on indirect evidence and therefore remains highly speculative. Because cleavage of cell cycle regulators occurs late in apoptosis by caspase-3-like activities in parallel with the dismantling of the transcription and translation machinery, caspase activation cannot trigger the normal mitotic program. For example, mitotic spindles do not form in apoptotic cells, distinguishing apoptosis from a mitotic catastrophe.

Limited substrate cleavage in terminal differentiation and hematopoiesis
In contrast to the rather speculative involvement of caspases in proliferation, there is an increasing body of evidence suggesting that caspases might act in cellular differentiation. A physiological role of caspases in this process has first been suggested for keratinocytes and lens fiber cells, in which the characteristic enucleation of the cells could be regarded somehow as a caspase-mediated incomplete apoptotic process. Caspases have also been implicated in erythropoiesis, because caspase inhibitors suppressed the nuclear extrusion process and consequent erythrocyte formation. Furthermore, caspase activation can be detected during thrombopoiesis and the fragmentation of proplatelets from megakaryocytes, without a concomitant induction of cell death. Both the incubation with peptide caspase inhibitors and the overexpression of Bcl-2 blocked proplatelet formation. Interestingly, in transgenic mice overexpressing Bcl-2 under the control of a hematopoietic cell-specific promoter, also a reduction in platelet formation is found, whereas the number of megakaryocytes remains unchanged. Finally, caspases might be required for differentiation processes also of nucleated cells such as macrophages and muscle cells. Elevated caspase activation is detectable in monocyes when they undergo M-CSF-stimulated macrophage differentiation. This is not only prevented by pharmacological caspase inhibitors, but also by the overexpression of Bcl-2 and p35. In myoblasts, homologous deletion of caspase-3 leads to a dramatic reduction in myofiber formation and decreased expression of muscle-specific proteins. Thus, all these lines of evidence suggest that caspases are not only required for cell death processes, but might also be capable of regulating nonapoptotic functions in certain cell types.

It is obvious that differentiation-related caspase activation must be tightly regulated to prevent cells from dying by apoptosis. During cellular differentiation, caspase activation is apparently either very limited, transient or localized. For instance, during megakaryocyte differentiation, the limited caspase activation is confined to dot-like structures. When senescent megakaryocytes die, however, caspase activation switches from a localized to a diffused and largely increased cytosolic activation. Also, little is known about the proteins cleaved by caspases during differentiation processes. Only a limited number of distinct substrates seem to be cleaved. For instance, in erythroblasts cleavage of PARP, lamin B and acinus was found, while the ICAD and GATA-1, a transcription factor essential for erythrocyte formation, remained intact. Interestingly, MST1 kinase was identified as a crucial caspase-3 effector in myoblast differentiation. As mentioned above, MST1 is cleaved and activated by caspase-3, and serves to enhance the activity of downstream MAP kinases that promote skeletal muscle differentiation. Expression of the truncated active kinase restored the differentiation phenotype in caspase-3 deficient myoblasts.
As discussed above, it remains currently unexplained as to how caspases could selectively cleave some targets without cleaving others. The compartmentalization of caspases, the duration of the caspase signal, or the coordinated expression of antiapoptotic molecules might play a role in the selectivity of caspase cleavage. It is also conceivable that low levels of caspase activity, such as those observed in differentiating cells, are associated with protective mechanisms. For instance, it was reported that the partial cleavage of Ras-GAP, a GTPase in the Ras signaling pathway, owing to low caspase activity first generates an N-terminal fragment that is antiapoptotic by activating the PI3K pathway.12 Increased caspase levels, in contrast, result in the further cleavage of Ras-GAP into two proapoptotic fragments. Thus, caspase cleavage of intracellular target proteins may strongly depend on the cellular context including the differentiation status. Clearly, much remains to be learned about a potential dual role of caspases in apoptosis and cellular differentiation. Characterization of the molecules that regulate this limited caspase activation and the relevant substrates will certainly provide exciting new insights into processes that, beyond cell death, might link caspase cleavage to important nonapoptotic biological processes.

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