Transworld Research Network
37/661 (2), Fort P.O., Trivandrum-695 023, Kerala, India

Apoptosis in the Retina, 2006: 1-11 ISBN: 81-7895-217-3
Editors: Alicia Torriglia and Patricia Crisanti-Lassiaz

1 Apoptosis and cell death

A. Ivana Scovassi
Istituto di Genetica Molecolare CNR, Via Abbiategrasso 207, 27100 Pavia, Italy

Abstract

Each minute, in a body a considerable number of cells undergo cell death. When a new cell replaces a dead cell, homeostasis is maintained. The balance between proliferation and death of a cellular population is altered when death events occur to an extent lower than normal, thus leading to cell accumulation disorders; on the contrary, increased cell death could be responsible for cell loss and related diseases. The elimination of cells that naturally contribute to tissue and organ homeostasis is defined as Programmed Cell Death, which generally occurs through the process of apoptosis.

Correspondence/Reprint request: Dr. A. Ivana Scovassi, Istituto di Genetica Molecolare CNR, Via Abbiategrasso 207, Pavia, Italy. E-mail: scovassi@igm.cnr.it

Introduction

The balance between cell proliferation and cell death is essential to maintain tissue homeostasis. Individual cells may commit suicide through a process known as Programmed Cell Death (PCD). The term Programmed Cell Death was first introduced by Lockshin and Williams and referred to the controlled cell death occurring during insect metamorphosis, as carefully detailed in a series of papers on Journal of Insect Physiology [1-5]. A number of observations revealed that cell death occurs in an ordered way throughout the embryogenesis and development both of vertebrates and invertebrates [6-10]. Different forms of PCD have been characterized, the most common of which is apoptosis. Kerr, Currie and Wyllie in 1972 first introduced the term *apoptosis* [11]: "*The term apoptosis is proposed for a hitherto little recognized mechanism of controlled cell deletion, which appears to play a complementary but opposite role to mitosis in the regulation of animal cell populations*". The word has a Greek origin, and means the falling off of leaves from trees or of petals from flowers, which are tightly controlled events, like the elimination of cells from an organism in due time. As emphasized by Fernandez-Flores et al. [12], the word *apoptosis* was found in a Spanish dictionary of medicine written in 1878. Interestingly, Mauro Degli Esposti revealed that Hippocrates designed as *apoptosis* the elimination of bone cells after a fracture, and that also Galen used this word to indicate falling of scabs [13].

Apoptosis: When?

The main conditions where apoptosis occurs are reported in Figure 1. Apoptosis is activated by appearance/disappearance of cell signals and by external stimuli in a number of physiological developmental conditions during the embryonic development, including the separation of the digits, metamorphosis and atrophy of tissues and organs, sexual differentiation and tissue turnover. In general, in many tissues at some stages of their development apoptosis provides the way of discarding redundant cellular material. The relevance of cell death in eye formation as well as the role of apoptosis in ocular diseases are discussed in this book.

Apoptosis can also be triggered by various external stimuli. Apoptosis is activated in mammalian cultured cells when they are exposed to inappropriate growth signals, such as serum starvation, growth factor deprivation and senescence. DNA-damaging agents and stress conditions such as heat shock, oxidants and free radicals are able to activate the apoptotic pathway(s). Also therapy-associated agents, i.e. chemotherapeutic drugs, gamma and UV radiation, are considered as apoptosis inducers. By consequence, since many anticancer drugs trigger the induction of apoptotic pathways, it is generally assumed that the activation of apoptotic pathways plays a relevant role in the killing of neoplastic cells [14].

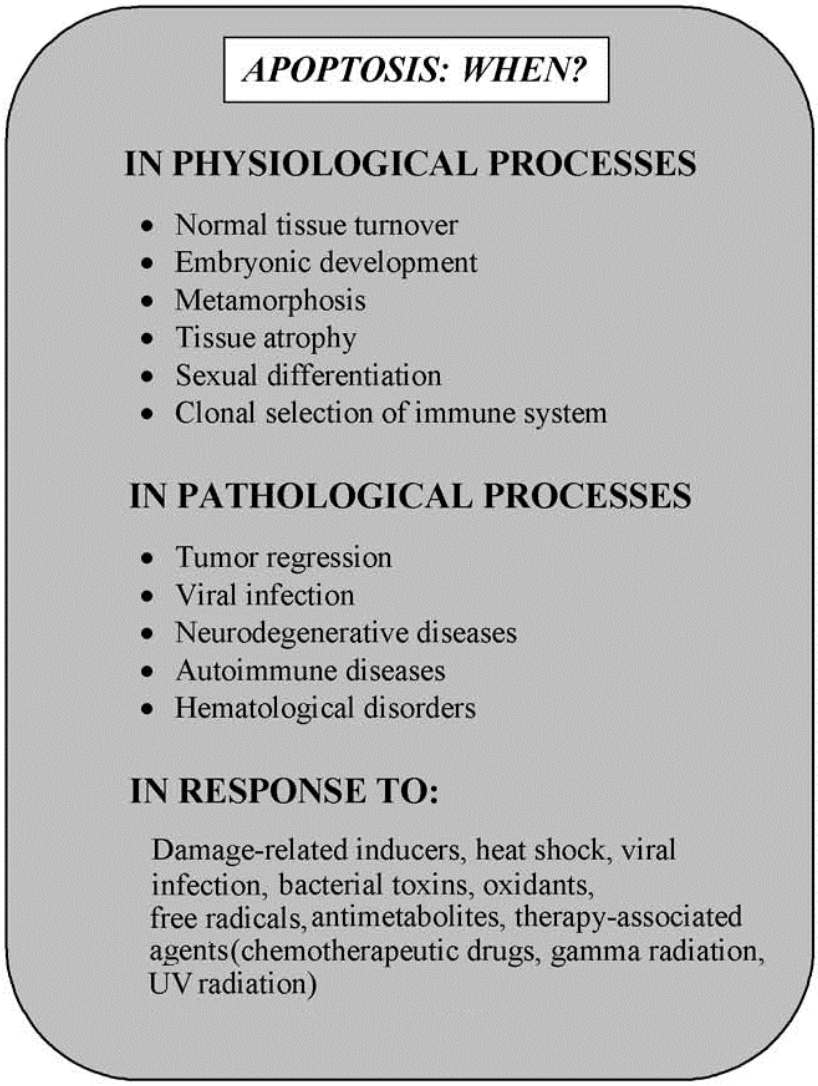

Figure 1. Occurrence of apoptosis in physiological/pathological processes and in response to external stimuli.

Apoptosis: How?

Apoptosis is an active process that is characterized by a number of histologically distinct steps [15-17], including cell shrinkage, nuclear condensation, membrane blebbing and clearance of apoptotic bodies by phagocytosis, and peculiar biochemical events, i.e. ordered DNA fragmentation and controlled protein cleavage. The most common hallmarks of apoptosis are reported in Figure 2. The morphological changes occurring during apoptosis lead to typical features visible at microscopic level, such as changes in the cellular membrane, chromatin condensation and fragmentation, and the formation of apoptotic bodies. The fate of apoptotic cells is to be engulfed by surrounding cells that are able to recognize apoptotic flags on the cell surface [18]. An overview of the methods to study apoptosis has been provided by Zakeri and Lockshin [19].

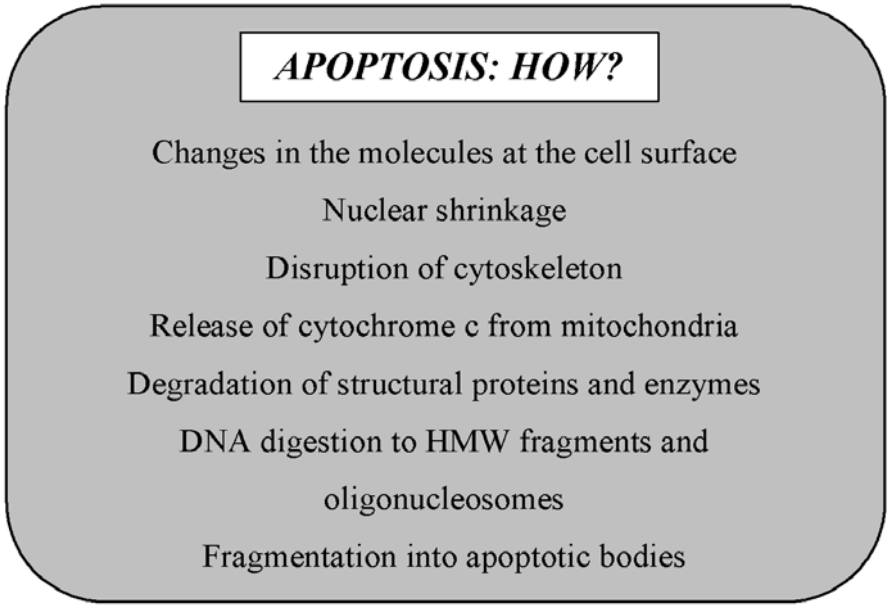

Figure 2. Morphological and biochemical hallmarks of apoptosis.

An example of different apoptotic features is shown in Figure 3, where Panel A illustrates the typical chromatin fragmentation caused by the treatment of HeLa cells with 100 μM etoposide for 3 h followed by a 24-h recovery. The dismantling of a cell via apoptosis requires the ordered cleavage of DNA and proteins [20]. DNA integrity is affected first by the formation of High Molecular Weight (HMW) DNA fragments (50-300 kb), which can be visualized by pulsed-field gel electrophoresis (PFGE). The most representative marker of apoptosis is still considered, even though not always occurring, DNA fragmentation at the internucleosomal region. This phenomenon originates multiples of 180 bp revealed as a ladder by conventional gel electrophoresis (Figure 3, panel B). As a consequence of DNA degradation, free termini are present in cellular DNA, which could be visualized by TdT-mediated-X-dUTP nick end labeling (TUNEL) procedure.

The nature of enzymes degrading DNA during apoptosis has not been completely elucidated. Data on endonucleases and DNases that play an active role in apoptotic DNA degradation have been extensively reviewed by Alicia Torriglia and collaborators [21, 22].

Protein degradation is the other biochemical marker of apoptosis. The core of protein degradation is represented by caspases, i.e. cysteine proteases that promote an orderly destruction of key structural and regulatory proteins. The discovery of the pro-apoptotic activity of Interleukin 1-Converting Enzyme (ICE) [23] promoted an enormous effort in identifying proteases playing an active role in apoptosis. Since the assumption of *Cell Suicide: ICE not fire* [24], a caspase family has been identified and for a long time it was believed that caspases are the only key apoptotic proteases.

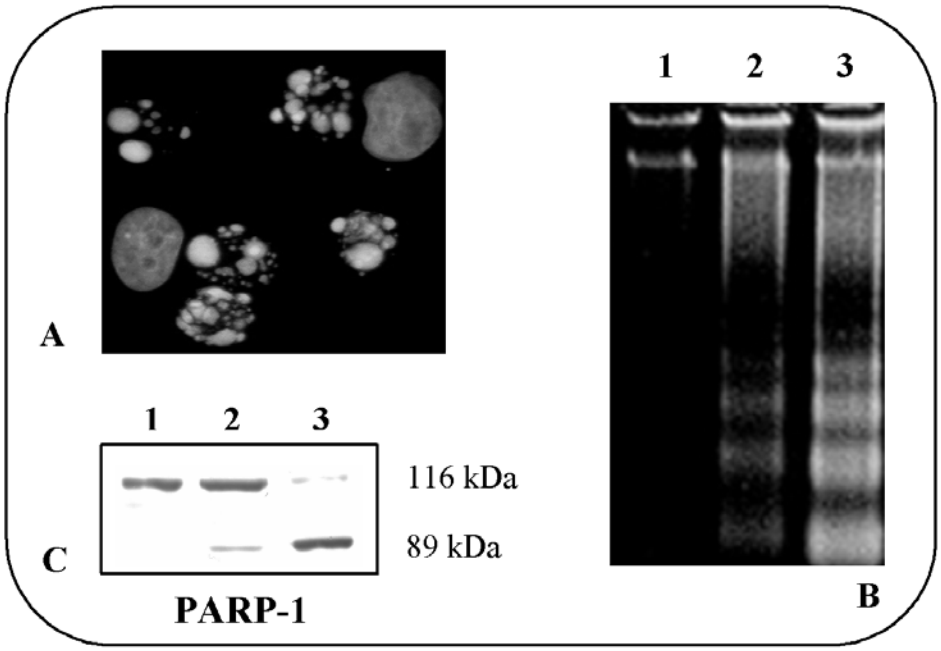

Figure 3. Visualization of typical apoptotic parameters. A: Apoptotic morphology of etoposide-treated HeLa cells stained with Hoechst 33258. B: DNA ladder from HL60 cells (1, control; 2, 3 treated with etoposide for increasing times). C: PARP-1 proteolysis in the same samples as B.

Caspases are synthesized in the cell as inactive zymogens, which are activated after a proteolytic event occurring in a cascade-like way. According to their activation timing, caspases can be defined as *initiator*s or *executioner*s. The processing of pro-apoptotic signals is controlled mainly through two pathways, the *extrinsic or receptor-mediated* and the *intrinsic or mitochondrial,* involving the assembly of constitutive factors into large protein complexes which then recruit and process initiator caspases. The vast literature on caspase structure and function has been widely reviewed [25-28].

Several targets of caspases have been described, including structural proteins (both cytoplasmic and nuclear), enzymes and cell cycle factors (for a detailed list of proteins that are cleaved by caspases see refs. [25, 26, 29-32]. The most studied target of proteases is the enzyme PARP-1 [33, 34], a 113 kDa protein that is cleaved into an 89 kDa and a 24 kDa fragment, as revealed by Western blot analysis (Figure 3, panel C).

Several reports demonstrate that cell death can proceed in the absence of caspases. Other proteases are engaged in cell dismantling, including cathepsins, calpains, serine proteases and granzymes [35-42]. Jäättelä and collaborators [43-46], among the leading scientists in this field, resumed the relevance of caspase-independent apoptosis in the following sentence: *Four deaths and a funeral: from caspases to alternative mechanisms.* Among the caspase-independent pathways, the best characterized involves lysosomal cathepsins,

thus suggesting an active role of the release of lysosomal enzymes into the cytosol, during apoptosis [47, 48].

Chipuk and Green in a recent review [42] have listed the peculiar features of caspase-independent cell death (CICD) by comparing them to the classical apoptotic hallmarks. A special form of CICD is Autophagy, which is characterized by self-digestion through the formation of cytoplasmic vacuoles, where some organelles are sequestered [reviewed in 49,50]. This degradative process appears to be conserved in eukaryotes and a number of genes involved in fundamental steps of the autophagic pathway have been identified. Autophagy proved to be associated with a growing number of pathological conditions [49,50].

In addition to the above described forms of cell death, cells could be eliminated by necrosis. Recently, it has been reported that necrosis can be considered as *a specific form of cell death* [51] that is not passive but requires some energy to occur [52]. As schematized in Figure 4, necrosis is characterized by cell swelling, rapid disruption of membrane, random degradation of DNA, organelle damage, dilatation of endoplasmic reticulum and cytoplasm vacuolization. In necrotic cells, membrane integrity is lost, leading to the release of cellular content, with resulting inflammation of surrounding tissues. The main

NECROSIS	APOPTOSIS
Morphological features	
↑ cell volume, swelling	↓ cell volume, shrinkage
no changes on membrane surface	changes on membrane surface
loss of membrane integrity	intact membrane blebbing
flocculation of chromatin	aggregation of chromatin
formation of vescicles	formation of apoptotic bodies
phagocytosis	phagocytosis
inflammatory response	no inflammatory response
Biochemical features	
loss of ion homeostasis	concerted enzymatic steps
no energy requirement	energy-dependent
random digestion of DNA	ladder
uncontrolled proteolysis	controlled proteolysis

Figure 4. Distinctive features of necrosis and apoptosis.

morphological and biochemical features which render necrotic cells distinguishable from apoptotic cells are shown in Figure 4. The microscopic observation of dying cells reveals a reduction in cell volume for apoptosis and a cell swelling for necrosis, accompanied by a different distribution of chromatin and changes in membrane structure. By the analysis of DNA and proteins, it has been shown that apoptotic cells undergo an ordered dismantling of macromolecules. In addition, Vandenabeele and coworkers demonstrated that, in contrast to apoptosis, during necrosis cells maintain the capacity to synthesize proteins [53].

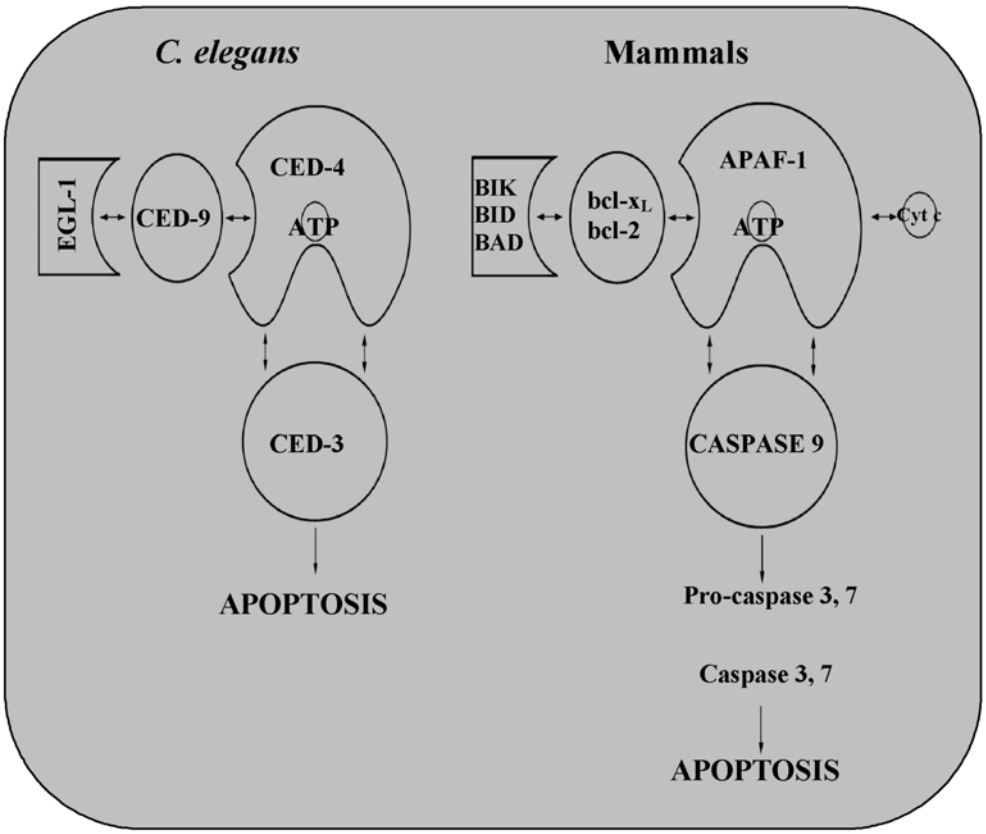

Figure 5. Comparison of the basic structure of the apoptosome in *C. elegans* and Mammals (adapted from Chinnaiyan [62]).

Apoptosis: A controlled process

The genetic control of apoptosis was first depicted in the nematode *Caenorhabditis elegans*, an excellent model for studying the basis of animal development. The considerable efforts in this field were rewarded in 2002 with the Nobel Prize in Physiology and Medicine to **Sydney Brenner, Robert Horvitz and John Sulston** for *their discoveries concerning genetic regulation of organ development and programmed cell death*. The evidence for a genetic control of life and death in *C. elegans* (extensively reviewed in [54-61]) represented the starting point in the definition of apoptosis in more complex

multicellular organisms and made it possible to progress in the apoptosis field. Three essential genes were identified: *ced* (cell death abnormal*)-3, ced-4, ced-9*, the latter being a negative regulator of the others. CED-4 protein is an activator of CED-3. These genes are essential for the ordered elimination of 131 of the 1090 cells occurring in a highly reproducible way during *C. elegans* development.

Most of the components of the apoptotic pathway proved to be evolutionary conserved and the essential death functions constitute the *heart and soul of the cell death machine*, the so-called *apoptosome* [62, 63]. Figure 5 shows the common mechanism and the core constituents of apoptosis. CED-3 is homologous to a caspase, CED-4 is the equivalent of Apaf-1, and CED-9 is homologous to death-suppressors such as Bcl-$_{XL}$ and Bcl-$_2$. The upstream nematode factor EGL-1 is a homologue of mammalian death-promoting proteins Bik, Bid, and Bad. ATP is relevant for the activation of the apoptotic machinery in both the organisms. As recently discussed by Michael Hengartner [64], another feature that is common to nematodes and Mammals is the fragmentation of mitochondria during apoptosis, possibly causing the release of crucial mitochondrial factors. This is a further evolutionary conserved aspect of apoptosis.

Going deeper into the strategies of a cell towards apoptosis, a basic question is: when a cell line is "committed" for the apoptotic process, is it able to respond in the same way to different death inducers? This point could be addressed by testing the same biological system under different experimental conditions. For example, we reported that HeLa cells treated with various inducers show comparable apoptotic end-points, i.e. chromatin condensation, DNA and protein cleavage, but activate different death pathways [65, 66], depending on the inducer. Moreover, the form of cell death induced by a particular agent could be dose- and -damage-dependent, thus indicating that there is a growing level of complexity within the cell when it has to be decided how to die.

Looking at apoptosis “through the eyes of clinicians”, it is obvious that a deregulation of such process could contribute to the ethiology of several diseases [67-69]. For example, tumor development can be ascribed to an uncontrolled balance between death and proliferation, thus resulting in an increased cell number mainly due to a failure of the apoptotic programme [14, 70-76]. In this respect, also tumor resistance to chemo- and radio-therapy may be ascribed to a deficiency in apoptosis induction. Conversely, loss of neurons in neurodegenerative disorders can be due to an excessive apoptosis [77-80], which is possibly responsible also for the dramatic decrease of lymphocytes in infectious diseases [81]. Of course, these considerations prompted many groups to try to obtain a beneficial modulation of apoptosis.

Concluding remarks

The idea of cell suicide in the philosophic universe was recently revisited by Federico Focher [82] with respect to the Schopenhauer's world, by Gerry Melino who explored the Camus's way of thinking [83], and by Jean Claude Ameisen in his book "La sculpture du vivant. Le suicide cellulaire ou la mort créatrice" [84].

The growing interest toward apoptosis prompted many groups to explore this complex field. International Societies, grouping researchers working on this field, have been founded, i.e. **European Cell Death Organization (ECDO)** and **International Cell Death Society**. Since the number of papers in this field dramatically increased in the past decade, two scientific journals were entirely devoted to Cell Death. **Cell Death & Differentiation** (first published in 1994) described its scope as follows: *The primary journal focused on the exciting field of programmed cell death and apoptosis; A single accessible source of information for both scientists and clinicians, keeping them up-to-date with advances in the field; Encompasses programmed cell death, cell death induced by toxic agents, differentiation and the interrelation of these with cell proliferation.* **Apoptosis** *is devoted to the rapid publication of innovative basic and clinically-oriented investigations into programmed cell death. It aims to stimulate both research on the basis of mechanisms of apoptosis and on its role in various human disease processes including: cancer, autoimmune disease, viral infection, AIDS, cardiovascular disease, neurodegenerative disorders, osteoporosis and ageing. The Editor-In-Chief recognises the need to encourage the development of clinical therapies against apoptosis-related diseases.*

Among the numerous books dedicated to this subject, we recommend *When cells die II*, 2004, R.A. Lockshin and Z. Zakeri (Eds.), Wiley-Liss, New York and *Apoptosis*, 2005, A.I. Scovassi (Ed.), Research Signpost, Kerala, India.

Acknowledgements

Research at the author's laboratory is supported by the Italian MIUR (FIRB Project RBNE0132MY and PRIN Project 2005058254).

References

1. Lockshin, R.A., and Williams, C.M. 1964, J. Insect. Physiol., 10, 643.
2. Lockshin, R.A., and Williams, C.M. 1965, J. Insect. Physiol., 11, 123.
3. Lockshin, R.A., and Williams, C.M. 1965, J. Insect. Physiol., 11, 601.
4. Lockshin, R.A., and Williams, C.M. 1965, J. Insect. Physiol., 11, 803.
5. Lockshin, R.A., and Williams, C.M. 1965, J. Insect. Physiol., 11, 831.
6. Saunders, J., 1966, Science, 154, 604.
7. Jacobson, M.D., Weil, M., and Raff, M.C. 1997, Cell, 88, 347.
8. Vaux, D.L., and Korsmeyer, S.J. 1999, Cell, 96, 245.
9. Zakeri, Z., and Lockshin, E.A. 2002, J. Immunol. Meth., 265, 3.

10. Zakeri, Z., and Lockshin, E.A. 2004, When cells die II, R.A. Lockshin and Z. Zakeri (Eds.), Wiley-Liss, New York, 3.
11. Kerr, J.F.R., Wyllie, A.H., and Currie, A.R., 1972, Br. J. Cancer, 26, 239.
12. Fernandez-Flores, A., Aguilera, B., Yau, P., and Oliva, H. 2002, Lancet, 359, 1072.
13. Degli Esposti, M. 1998, Cell Death Differ., 5, 719.
14. Brown, J.M., and Attardi, L.D. 2005, Nat. Rev. Cancer, 5, 231.
15. Wyllie, A.H., Kerr, J.F., and Currie, A.R. 1980, Int. Rev. Cytol., 68, 251.
16. Wyllie, A.H., Kerr, J.F.R., and Currie, A.R. 1987, Int. Rev. Cytol., 17, 755.
17. Arends, M.J., and Wyllie, A.H. 1991, Int. Rev. Exp Pathol., 32, 223.
18. Dini, L. 2005, Apoptosis, A.I. Scovassi (Ed.), Research Signpost, Kerala, India, 107.
19. Zakeri, Z., and Lockshin, E.A. 2004, When cells die II, R.A. Lockshin and Z. Zakeri (Eds.), Wiley-Liss, New York, 27.
20. Negri, C., Bernardi, R., Donzelli, M., Prosperi, E., and Scovassi, A.I. 1996, Cell Death Differ., 3, 425.
21. Scovassi, A.I., and Torriglia, A. 2003, Eur. J. Histochem., 47, 185.
22. Torriglia, A., and Padrón, L. 2005, Apoptosis, A.I. Scovassi (Ed.), Research Signpost, Kerala, India, 27.
23. Miura, M., Zhu, H., Rotello, R., Hartwieg, E.A., and Yuan, J. 1993, Cell, 75, 653.
24. Barinaga, M., 1999, Science, 280, 32.
25. Earnshaw, W.C., Martins, L.M., and Kaufmann, S.H. 1999, Annu. Rev. Biochem., 68, 383.
26. Chang, H.Y., and Yang, X. 2000, Microbiol. Mol. Biol. Rev., 64, 821.
27. Adams, J.M. 2003, Genes Dev., 17, 2481.
28. Fuentes-Prior, P., and Salvesen, G.S. 2004, Biochem. J., 384, 201.
29. Cain, K., Bratton, S.B., and Cohen, G.M. 2002, Biochimie, 84, 203.
30. Riedl, S.J., and Shi, Y. 2004, Nature Rev. Mol. Cell Biol., 5, 897.
31. Nicholson, D.W. 1999, Cell Death Differ., 6, 1028.
32. Fischer, U., Jänicke, R.U., and Schulze-Osthoff, K. 2002, Cell Death Differ., 10, 76.
33. Scovassi, A.I., and Poirier, G.G. 1999, Mol. Cell Biochem., 199, 125.
34. Soldani, C., and Scovassi, A.I. 2002, Apoptosis, 7, 321.
35. Wyllie, A.H., and Golstein, P. 2001, Proc. Natl. Acad. Sci. USA, 98, 11.
36. Grabarek, J., Du, L., Johnson, G.L., Lee, B.W., Phelps, D.J., and Darzynkiewicz, Z. 2002, Cell Cycle, 1, 124.
37. Adams, J.M. 2003, Genes Dev., 17, 715.
38. Kaufmann, S.H., and Hengartner, M.O. 2001, Trends Cell Biol., 11, 526.
39. Abraham, M.C., and Shaham, S. 2004, Trends Cell Biol., 14, 184.
40. Guimarães, C.A., and Linden, R. 2004, Eur. J. Biochem., 271, 1638.
41. Hong, S.J., Dawson, T.M., and Dawson, V.L. 2004, Trends Pharmacol. Sci., 25, 259.
42. Chipuk, J.E., and Green, D.R. 2005, Nat. Rev. Mol. Cell Biol., 6, 268.
43. Leist, M., and Jäättelä, M. 2001, Nat. Rev. Mol. Cell Biol., 2, 589.
44. Mathiasen, I.S., and Jäättelä, M. 2002, Trends Mol. Med., 8, 212.
45. Jäättelä, M., and Tschopp, J. 2003, Nat. Immunol., 4, 416.
46. Jäättelä, M. 2004, Oncogene, 23, 2746.
47. Guicciardi, M.E., Leist, M., and Gores, G.J. 2004, Oncogene, 23, 2881.
48. Guicciardi, M.E., and Gores, G.J. 2005, Apoptosis, A.I. Scovassi (Ed.), Research Signpost, Kerala, India, 57.

49. Marino, G., and Lopez-Otin, C. 2004, Cell Mol. Life Sci., 61, 1439.
50. Shintani, T., Klionsky, D.J. 2004, Science, 306, 990.
51. Proskuryakov, S.Y., Konoplyannikov, A.G., and Gabai, V.L. 2003, Exp. Cell Res., 283, 1.
52. Chiarugi, A. 2005, Apoptosis, A.I. Scovassi (Ed.), Research Signpost, Kerala, India, 13.
53. Saelens, X., Festjens, N., Parthoens, E., Vanoverberghe, I., Kalai, M., van Kuppeveld, F., and Vandenabeele, P. 2005, J. Cell Biol., 168, 545.
54. Ellis, R.E., Yuan, J.Y., and Horvitz, H.R. 1991, Annu. Rev. Cell Biol., 7, 663.
55. Hengartner, M.O., and Horvitz, H.R. 1994, Curr. Opin. Genet. Dev., 4, 581.
56. Metzstein, M.M., Stanfield, G.M., and Horvitz, H.R. 1998, Trends Genet., 14, 410.
57. Horvitz, H.R. 1999, Cancer Res., 59, S1701.
58. Fraser, A.G. 1999, Cancer Metastasis Rev., 18, 285.
59. Stergiou, L., and Hengartner, M.O. 2004, Cell Death Differ., 11, 21.
60. Reddien, P.W., and Horvitz, H.R. 2004, Annu. Rev. Cell. Dev. Biol., 20, 193.
61. Kinchen, J.M., and Hengartner, M.O. 2005, Curr. Top. Dev. Biol., 65, 1.
62. Chinnaiyan, A.M. 1999, Neoplasia, 1, 5.
63. Adams, J.M., and Cory, S. 2002, Curr. Biol., 14, 2481.
64. Hengartner, M.O. 2005, Nature, 433, 692.
65. Torriglia, A., Negri, C., Chaudun, E., Prosperi, E., Courtois, Y, Counis, M.F., and Scovassi, A.I. 1999, Cell Death Differ., 6, 234.
66. Gorrini, G., Donzelli, M., Torriglia, A., Supino, R., Brison, O., Bernardi, R., Negri, C., Denegri, M., Counis, M.F., Ranzani, G.N., and Scovassi, A.I. 2003, Int. J. Mol. Med., 11, 737.
67. Narula, J., Kharbanda, S., and Sluyser, M. 2001, Apoptosis, 6, 5.
68. Reed, J.C. 2001, Trends Mol. Med., 7, 314.
69. Greenwood, E. 2004, Cell Death Differ., 11, S1.
70. Raff, M. 1998, Nature, 396, 119.
71. Wyllie, A.H., Bellamy, C.O., Bubb, V.J., Clarke, A.R., Corbet, S., Curtis, L., Harrison, D.J., Hooper, M.L., Toft, N., Webb, S., and Bird, C.C. 1999, Br. J. Cancer., 80 S1, 34
72. Kaufmann, S.H., and Gores, G.J. 2000, BioEssays, 22, 1007.
73. Evan, G.I., and Vousden, K.H. 2001, Nature, 411, 342.
74. Zörnig, M., Hueber, A., Baum, W., and Evan, G. 2001, Biochim. Biophys. Acta, 1551, F1.
75. Hajra, K.M., and Liu, J.R. 2004, Apoptosis, 9, 691.
76. Zhivotovsky, B., and Kroemer, G. 2004, Nature Rev. Mol. Cell Biol., 5, 752.
77. Kanazawa, I. 2001, Trends Mol. Med., 7, 339.
78. Gasic, G.P., and Nicotera, P. 2003, Toxicol. Lett., 139, 221.
79. Okada, H., and Mak, T.W. 2004, Nature Rev. Cancer, 4, 592.
80. Crighton, D., and Ryan, K.M. 2004, Biochim. Biophys. Acta, 1705, 3.
81. Dockrell, D.H. 2001, J. Infection, 42, 227.
82. Focher, F. 2002, Apoptosis, 7, 285.
83. Melino, G. 2002, Cell Death Differ., 9, 347.
84. Ameisen, J.C. 1999, La sculpture du vivant. Le suicide cellulaire ou la mort créatrice, Edition du Seuil, Paris.

The International Cell Death Society promulgates research and clinical information on the broad topic of cell death, including apoptosis, autophagy, necrosis, necroptosis, and other variants. Meeting Information: Meeting Information. ICDS Contact (secretary). Meeting Contact (webmaster). Registration, Lodging, and Abstracts.Â 2020 meeting new trends in cell death may 21-MAY 23, 2020 glenburn lodge, kromdraai, johannesburg, south africa see â€œNext meetingâ€ and watch for updates! Letters for visas. If you need a letter for a visa, please your passport name and title of abstract or any other required information to webmaster@celldeath-apoptosis.org. Registration without dinner cruise (New! April 15). Apoptosis (from Ancient Greek á¼€Ï€ÎŒÏ„Ï‰ÏƒÎ¹Ï‚, "falling off") is a form of programmed cell death that occurs in multicellular organisms. Biochemical events lead to characteristic cell changes (morphology) and death. These changes include blebbing, cell shrinkage, nuclear fragmentation, chromatin condensation, chromosomal DNA fragmentation, and global mRNA decay. The average adult human loses between 50 and 70 billion cells each day due to apoptosis. For an average human child between the ages of 8 to 14