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A Brief History of Apoptosis: From Ancient to Modern Times

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Key Words
Apoptosis · Cell death · Necrosis · Programmed cell death · History of medicine

Summary
The purpose of this article is to sketch the evolution of research on cell death and apoptosis from ancient to modern times. Early use of the term can be found in the texts of Hippocrates, whereas the first description of apoptotic cell death should be attributed to Rudolf Virchow. Glucksman, in 1951, rediscovered and reviewed cell death during embryonic development. Milestone discoveries in biology in the 20th century led biologists to the discovery of apoptotic mechanisms, soon after the definition of apoptosis by Kerr in 1972. The involvement of programmed cell death in the pathogenesis of various diseases and abnormalities gave a huge boost in the research of apoptosis. Nowadays, research is focused on the elucidation of apoptotic mechanisms, since the possibility of modulating cell death by targeting specific factors involved in the whole process could be the key for cure of diseases such as cancer, Alzheimer's disease, and AIDS.

Schlüsselwörter
Apoptose · Zelltod · Nekrose · Programmierter Zelltod · Geschichte der Medizin

Zusammenfassung
Zweck dieses Artikels ist es, die Evolution der Erforschung von Zelltod und Apoptose von der Antike bis zur Gegenwart zu umreißen. Der Begriff Apoptose findet frühe Erwähnung in den Texten von Hippokrates. Der apoptotische Zelltod wurde jedoch erstmals von Rudolf Virchow beschrieben. 1951 wurde der Zelltod während der Embyonalentwicklung von Glucksman erneut entdeckt und analysiert. Entscheidende biologische Erkenntnisse des 20. Jahrhunderts führten kurz nach der Definition der Apoptose von Kerr im Jahre 1972 zur Entdeckung apoptotischer Mechanismen. Die Beteiligung des programmierten Zelltodes an der Pathogenese verschiedener Erkrankungen und Abnormalitäten gab der Apoptoseforschung einen enormen Aufschwung. Heute konzentriert sich die Forschung auf die Aufklärung apoptotischer Mechanismen, da eine mögliche Modulierung des Zelltodes durch die gezielte Einflussnahme auf spezifische Faktoren des Apoptoseprozesses der Schlüssel zur Heilung bestimmter Krankheiten wie Krebs, Morbus Alzheimer und AIDS sein könnte.

Introduction – Origin and Etymology of the Term 'Apoptosis'

The Greek word 'apoptosis' is compound, and was initially used to describe the programmed shedding of leaves in autumn. The first use of the term 'apoptosis' in Medicine should be attributed to Hippocrates of Cos [1] (table 1) who used this word to describe gangrene resulting from treatment of fractures with bandages [2]. It is interesting to note that almost 2,000 years before the reuse of the term by Kerr et al. [3], Hippocrates used this word exactly to describe a physiological form of cell/tissue death.

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Table 1. Summary of the history of apoptosis

Author [Ref.]	Year	Contribution
Hippocrates of Cos [2]	4th century BC	first use of the term 'apoptosis'
Vogt [6]	1842	first report of cell death
Virchow [7]	1860	description of 2 types of cell death (necrosis and necrobiosis); the term necrobiosis morphologically described apoptosis
Flemming [10]	1885	description of apoptotic death as the result of mechanical forces and chemical intracellular changes ('chromatolysis')
Cohnheim [9]	1889	use of the term 'coagulation necrosis'
Metchnikov [11]	1892	discovery of phagocytosis
Perez [12]	1910	work concerning cell death in metamorphosis of the blowfly *Calliphora erythrocephala*
Graeper [13]	1914	description of chromolysis as a marker of dying cells
Glucksmann [14]	1951	hallmark paper describing different types of cell death, including 'karyorrhexis' and 'karyopyknosis'
Lockshin and Williams [23]	1965	introduction of the term 'programmed cell death' to characterize a sequence of genetically controlled events which cause cells to die during embryonic development
Saunders [24]	1966	description of death in embryonic systems
John Kerr [17]	1965	description of 'shrinkage necrosis' as a particular type of cell death
Williams et al. [18]	1974	description of a connection between DNA degradation by endonucleases and mammalian cell death ('DNA ladder')
Different groups of authors [34–50]	1980–1994	identification of genes controlling cell death
Different groups of authors [52–57]	1985–today	recognition of the role of apoptosis in disease and the use of mechanisms of apoptosis in therapeutics

Studies on Cell Death during the 18th and 19th Century

A hallmark in the history of cytology and pathology was the establishment of the cell theory by Schleiden and Schwann [4, 5]. However, the first report of cell death is attributed to Karl Vogt [6] who reported cell death in the notochord and adjacent cartilage of metamorphic toads. Almost 2 decades later, Rudolph Virchow, in his lectures on Cellular Pathology [7], referred to 2 types of cell death, necrosis and necrobiosis, with distinct characteristics between them. Virchow, under the term 'necrobiosis', described apoptosis morphologically – a process of cell degeneration characterized by tissue softening, which characteristically preserved the outer form of the tissues until 'absolutely nothing of the previously existing tissues is preserved'. The term 'apoptosis' can also be found in a Spanish medical dictionary published at the end of the 19th century [8].

After Vogt and Virchow, numerous studies on cell death were published until the end of the 19th century. A closer look at all those studies could convince someone to conclude that a few of them, indeed, described typical forms of apoptotic cell death. Anatomists and pathologists of the 19th century mainly worked on tadpoles and insects as well as in embryogenesis using the notochord as a model. Among those studies, the work by Julius Cohnheim [9] and Walther Flemming [10] is the most significant. Julius Cohnheim [9] was the first to introduce the term 'coagulation necrosis'. However, a typical form of apoptotic death was first described by Flemming [10]; he was the first to suggest that cell death was not just a result of mechanical forces but also of chemical changes within the cells. He first used the word 'chromatolysis' to describe dying cells whose chromatin disintegrated. More specifically, he reported the presence of 'half-moons' of heterochromatin, and the successive disruption of cell nuclei surrounded by a rim of cytoplasm in the cavity of the follicle. Today, DNA fragmentation is one of the hallmark characteristics of apoptosis.

The Concept of Cell Death during 20th Century: The Work by Metchnikov and Perez, and the Hallmark Paper by Glucksmann

In the early beginning of the 20th century, Ilya Metchnikov [11] and Charles Perez [12] made important contributions in the field of cell death. Graeper [13] in 1914, working on the yolk sac, also referred to chromatolysis as a marker of dying cells, as Flemming did; however, due to the dual meaning of the term – neurologists used the same word to describe the collapse of Nissle substance after the transaction of the neural axon – Graeper's studies remained somehow unnoticed.

The first attempt to list all forms of cell death in vertebrate ontogeny is attributed to Glucksmann (1951) [14]. In his classic paper, different types of cell death are described; among them, 'karyorrhexis' (nuclear fragmentation) and 'karyopyknosis' (condensation of nuclei) resemble apoptotic cell death morphology. A few years later, De Duve [15] discovered and described lysosomes, a cell structure that plays a vital role during pathological cell death. In early 1960s, Bellairs [16] reported the characteristics of developmental cell death under the electron microscope.

The Work by John Kerr

The 1970s were the most important decade in the chronicle of apoptosis. John Kerr [17] described a type of cell death under the term of 'shrinkage necrosis'. His studies began with the observation of rapid shrinkage of liver tissue followed by an interruption of portal venous supply; during his experiments, Kerr observed hepatocytes which 'converted into small round masses of cytoplasm that often contained specks of condensed nuclear chromatin'. He was able to differentiate this type of cell death from necrosis histologically and by electron microscopy; it was quite different from necrosis, since neither neighboring cells were affected nor inflammation was present. Shrinkage necrosis was also described in other tissues and by other researchers.

The term 'apoptosis' was coined to that type of cell death, and it was described as a normal cellular procedure [3]. Subsequently, the connection of DNA degradation by endonucleases and mammalian cell death was described – known today as 'DNA ladder' [18] – whereas in 1980, Wyllie [19] connected this phenomenon with the apoptosis of thymocytes during glucocorticoid treatment. In 1997, DFF/CAD was identified as the major endonuclease that plays a key role in DNA degradation [20]. The 'DNA ladder' was the first marker of apoptosis, and various techniques were developed in order to identify this specific characteristic [21]. A second important marker of apoptosis was the exposition of phosphatidylserine on the surface of apoptotic cells [22].

From the Morphology to the Genetics of Programmed Cell Death

The concept of the genetic control of cell death was extremely attractive. In 1965, a paper by Lockshin and Williams [23] introduced for the first time the term 'programmed cell death' to characterize a sequence of genetically controlled events which cause cells to die during embryonic development. Their results were in agreement with the views of Saunders [24] who published a paper concerning death in embryonic systems 1 year later, and the results by Tata [25] who proved the need for RNA synthesis in the process of cell death in the regression of the tadpole tail. Saunders [24], characteristically, noted that 'the death clock is ticking', implying directly a controlled regulation of cell death.

Animal Models for the Study of Programmed Cell Death: Caenorhabditis elegans and Drosophila melanogaster

The application of modern genetic techniques, especially after the invention of recombinant DNA technology in the early 1970s, gave insight into the 'black box' of genetic control of cell death. In 1977, Sulston and Horvitz [26], using as an animal model *Caenorhabditis elegans,* reported that almost 13% of somatic cells in the embryo of this worm die in a short period of time. In 1982, Horvitz et al. [27] managed to identify the first cell death gene, named *ced-3* (from the initials *c*ell *d*eath). Since then, a many genes were found to control cell death. The discovery of cell death genes (such as the *reaper*) in *Drosophila melanogaster* was also a very important step in the field of programmed cell death [28]. HID and Grim were later identified as promoters of apoptosis. Extensive studies have been performed on the formation of Drosophila's eye and the *Hippo* transduction signal pathway.

The Role of Apoptosis in the Immune and Nervous System

The intracellular control of programmed cell death has been extensively studied in the maturation and function of the immune and nervous system. Research on the maturation of T and B lymphocytes has shown that apoptosis plays a crucial role in the negative selection of T cells, a process taking place in the thymus gland, and the formation of the T cell [29]. Similarly, more than 50% of neurons die during the embryo development in vertebrates, mainly during the time of neuronal migration [30].

Cell death has also been studied during the activation of lymphocytes and the process of killing of target cells by cytotoxic lymphocytes. The first identification of apoptosis in lymphocytes after the treatment with alkylating agents was done by Matyasova et al. [31]. Duvall et al. [32] reported the role of macrophages in the detection of apoptotic cells, whereas in 1991, Poe et al. [33] isolated a cytotoxic lymphocyte enzyme that mediated cell death (granzyme b).

The Identification of Human Genes Involved in Programmed Cell Death

Vaux et al. [34], in 1988, identified as a participant in the genetic control of cell death *bcl-2* – a gene that was initially involved in B cell lymphoma – and showed that *bcl-2* could inhibit cell death, for which reason it was characterized as an anti-apoptotic gene. In 1992, Vaux et al. [35] showed that *bcl-2* could inhibit cell death in *C. elegans*, whereas in 1994, Hengartner et al. [36] showed that *ced-9* was homologous to *bcl-2*. Since its discovery, numerous genes homolog to *bcl-2* were identified, such as *bax*, *bcl-x*, *bcl-xL* and *bcl-Xs*, *bak*, *Mcl-1*, *bad*, etc.

A second gene involved in apoptosis, which was identified later than *bcl-2* was *p53*; Yonish-Ruach et al. [37] showed that p53 could induce apoptosis of myeloid leukemic cells. Extensive research has been conducted on the role and functions of this gene and especially on its mutant forms which have been connected to various forms of cancer.

c-myc was a third gene involved in the pathways of apoptosis [38]. This gene was discovered through its homology with *v-myc*, a virus oncogene which causes myelocytomatosis in birds. More genes, homologues to *c-myc*, have been discovered since then, creating a new gene family, the c-myc family, which plays an important role in apoptosis [39].

A 4th important discovery in the field of the genetic control of apoptosis was the *Fas/APO-1* gene [40]. *Fas/APO-1* initially

was identified to be a tumor suppressor gene, and it was later connected with the destruction of healthy cells when the Fas ligand interacts with its receptor [41]. It was well known that anti-Fas antibodies could cause tumor regression, whereas 2 years later, in 1991, Itoh et al. [40] cloned the *fas* gene. The *Fas/APO-1* gene was found to code for a membrane receptor, CD95, a member of the TNF receptor superfamily. Watanabe et al. [42], in 1992, reported that defects in Fas antigen were responsible for lymphoproliferative disorders in mice, pointing to the important role of Fas in the development and function of the immune system. Research on the pathway that is activated after the interaction of FasL with the Fas receptor has shown that the transduction of the death signal is mediated by a protein adaptor named FADD [43], which, in turn, activates proteases of the ICE superfamily, caspases. Interleukin converting enzyme (ICE) proteases were first identified in 1992 by Thornberry et al. [44] and Cerretti et al. [45]. The first caspase which was identified to interact with FADD and the Fas receptor pathway was caspase 8 [46]. A broad gene family of caspases have been identified in mammals and in *Drosophila*. Finally, the identification of IAP genes [47] was another important discovery in the field of apoptosis. The next step in resolving the apoptosis puzzle was the identification of possible interactions between different genes and the comparison between apoptotic patterns of different organisms. It was well known that programmed cell death had common characteristics in vertebrates and invertebrates. Whitten [48], in 1969, had already noticed the similarities of cell death in the formation of the limb in insects and in vertebrates. In 1992, Vaux et al. [35] demonstrated that *bcl-2* could inhibit cell death in *C. elegans*. In 1993, Yuan et al. [49] identified *ced-3*, a gene homolog to ICE, whereas 1 year later, Hengartner et al. [36] identified *ced-9,* a gene of *C. elegans* which was homolog to *bcl-2*.

A characteristic example of the interaction between the pre-referred genes is the association of the bcl-2 gene family with p53, and the pre-referred association of the Fas/APO-1/CD95 receptor with caspases. Chiou et al. [50] showed in 1994, that *p53*-induced apoptosis was blocked by *bcl-2*. *p53* is shown to interact with many members of the bcl-2 family such as *bax*, *bcl-XL*, and BH3 proteins.

The Role of Apoptosis in Disease, and the Use of Mechanisms of Apoptosis in Therapeutics

The role of apoptosis in the pathogenesis of various pathologic conditions has also been extensively investigated. Apoptosis seems to play an important role in cancer, HIV-1 infection, and other tumor-inducing virus infections such as EBV, various autoimmune diseases, neurodegenerative disorders such as Alzheimer's, Huntington's, and Parkinson's disease, and in ischemia. In each case, either apoptosis is abnormally inhibited (for example, in cancer), or it is triggered as in the case of HIV-1 infection. In 1973, Danilevicius [51] in a short paper suggested for the first time a possible role of apoptotis in cancer, whereas in 1985, Clouston et al. [52] hypothesized that apoptosis may be used to counter viruses. Strasser et al. [53] showed that inhibition of cell death in lymphocytes could lead to autoimmune diseases, suggesting a role of apoptosis in lymphoproliferative disorders. In 1995, Roy et al. [54] suggested the role of apoptotic genes in neurodegenerative disease in patients with spinal muscular atrophy. The complete elucidation of genes and proteins involved in each apoptotic procedure may provide targets for therapy [55]; for example, in the case of cancer, the use of apoptotic agents could enhance the cytotoxicity of antitumor agents [56, 57].

References

1 André N: Hippocrates of Cos and apoptosis. Lancet 2003;361:1306.
2 Hippocrates of Cos: Mochlicon; in Hatzopoulos O (ed): Orthopaedics. The complete work of Hippocrates, vol. 12 (text in Ancient Greek and translated into modern Greek). Athens, Kaktos, 1992, chapter 35, pp. 281–282.
3 Kerr JFR, Wyllie AH, Curie AR: Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer 1972;26:239–257.
4 Schleiden, MJ: Beiträge zur Phytogenesis; in Müller J (ed): Archiv für Anatomie, Physiologie und wissenschaftliche Medicin. Berlin, 1838, pp. 137–176.
5 Schwann T: Mikroskopische Untersuchungen über die Übereinstimmung in der Struktur und dem Wachsthum der Thiere und Pflanzen. Berlin, Sander, 1839.
6 Vogt K: Untersuchungen über die Entwicklungsgeschichte der Geburtshelerkröte (Alytes obstretricians). Solothurn, Jent und Gassmann, 1842, p. 105.
7 Virchow R: Lecture XV. Passive processes, fatty degeneration; in Virchow R (ed): Cellular Pathology as Based upon Physiological and Pathological Histology (translated in English by Chance F and Cantab MB). London, John Churchill, 1860, p. 318.
8 Fernandez-Flores A, Aguilera B, Yau P, Oliva H: An old meaning of the word apoptosis. Lancet 2002;359:1072.
9 Cohnheim J: Lectures on Cellular Pathology. Sect II, ed. 2 (translated from German by AB McKee. London, New Sydenham Society, 1889.
10 Flemming W: Über die Bildung von Richtungsfiguren in Säugethiereiern beim Untergang Graaf'scher Follikel. Arch Anat Physiol 1885;221–244.
11 Metchnikoff E: La phagocytose musculaire. I. Atrophie des muscles pendant la transformation des batraciens. Ann Inst Pasteur 1892;6:1–12.
12 Pérez C: Recherches histologiques sur la métamorphose des muscides (Calliphora erytrocephala Mg). Arch Zool Exper Gen 5e Série 1910;4:1–274.
13 Graeper L: Eine neue Anschauung über physiologische Zellausschaltung. Arch Zellforschung 1914;2:373–394.
14 Glucksmann A: Cell deaths in normal vertebrate ontogeny. Biol Rev Camb Phil Soc 1951;26:59–86.
15 De Duve C: The lysosomes, a new group of cytoplasmic granules. J Physiol (Paris) 1957;49:113–115.
16 Bellairs R: Cell death in chick embryos as studied by electron microscopy. J Anat 1961;95:54–60.
17 Kerr JFR: A histochemical study of hypertrophy and ischaemic injury of rat liver with special reference to changes in lysosomes. J Pathol Bacteriol 1965;90:419–435.
18 Williams JR, Little JB, Shipley WU: Association of mammalian cell death with a specific endonucleolytic degradation of DNA. Nature 1974;252:754–755.
19 Wyllie AH: Glucocorticoid-induced thymocyte apoptosis is associated with endogenous endonuclease activation. Nature 1980;555–556.
20 Liu XS, Zou H, Slaighter C, Wang XD: DFF, a heterodimeric protein that functions downstream of caspase-3 to trigger DNA fragmentation during apoptosis. Cell 1997;89:175–184.
21 Gavrieli Y, Sherman Y, Ben-Sasson SA: Identification of PCD in situ via specific labelling of nuclear DNA fragmentation. Cell Biol 1992;119:493–501.

22 Fadok VA, Voelker DR, Campbell PA, Cohen JJ, Bratton DL, Henson PM: Exposure of phosphatydilserine on the surface of apoptotic lymphocytes triggers specific recognition and removal by macrophages. J Immunol 1992;148:2207–2216.
23 Lockshin RA, Williams CM: Programmed cell death. II. Endocrine potentiation of the breakdown of the intersegmental muscles of silkworms. J Insect Physiol 1965;11:803–809.
24 Saunders JW Jr: Death in embryonic systems. Science 1966;154:604–612.
25 Tata JR: Requirement for RNA and protein synthesis for induced regression of the tadpole tail in organ culture. Dev Biol 1966;13:77–94.
26 Sulston J, Horvitz HR: Postembryonic cell lineages of the nematode *Caenorhabditis elegans*. Dev Biol 1977;56:110–156.
27 Horvitz HR, Ellis HM, Sternberg PW: Programmed cell death in nematode development. Neurosci Comment 1982;1:56–65.
28 White K, Grether ME, Abrams JM, Young L, Farrell K, Steller H: Genetic control of programmed cell death in Drosophila. Science 1994;264:677–683.
29 Von Boehmer H: Positive selection of lymphocytes. Cell 1994;76:219–228.
30 Cowan WM, Fawcett JW, O'Leary DDM, Stanfield BB: Regressive events in neurogenesis. Science 1984;225:1258–1265.
31 Matyasova J, Skalka M, Cejkova M: Regular character of chromatin degradation in lymphoid tissues after treatment with biological alkylating agents in vivo. Folia Biologica 1979;25:380–388.
32 Duvall E, Wyllie AH, Morris RG: Macrophage recognition of cells undergoing programmed cell death (apoptosis). Immunology 1985;56:351–358.
33 Poe M, Blake JT, Boulton DA, Gammon M, Sigal NH, Wu JK, Zweerink HJ: Human cytotoxic lymphocyte granzyme characterization of substrate and inhibitor specificity. J Biol Chem 1991;266:98–103.
34 Vaux DL, Cory S, Adams JM: Bcl-2 gene promotes haemopoietic cell survival and cooperates with c-myc to immortalize pre-B cells. Nature 1988;335:440–442.
35 Vaux DL, Weissman IL, Kim SK: Prevention of programmed cell death in Caenorhabditis elegans by human bcl-2. Science 1992;258:1955–1957.
36 Hengartner MO, Horvitz HR: C. elegans cell survival gene ced-9 encodes a functional homolog of the mammalian proto-oncogene bcl-2. Cell 1994;76:665–676.
37 Yonish-Ruach E, Resnitzky D, Lotem J, Sachs L, Kimchi A, Oren M: Wild-type p53 induced apoptosis of myeloid leukaemic cells that is inhibted by interleukin-6. Nature 1991;353:345–347.
38 Evan GI, Wyllie AH, Gilbert CS, Littlewood TD, Land H, Brooks M, Waters CM, Penn LZ, Hancock DC: Induction of apoptosis in fibroblasts by c-myc protein. Cell 1992;69:119–128.
39 Dang CV, O'Donnell KA, Zeller KI, Nguyen T, Osthus RC, Li F: The c-myc target gene network. Semin Canc Biol 2006;16:253–264.
40 Itoh N, Yonehara S, Ishii A, Yonehara M, Mizushima S, Sameshima M, Hase A, Seto Y, Nagata S: The polypeptide encoded by the cDNA for human cell surface antigen Fas can mediate apoptosis. Cell 1991;66:233–243.
41 Alderson MR, Tough TW, Davis-Smith T, Braddy S, Falk B, Schooley KA, Goodwin RG, Smith CA, Ramsdell F, Lynch DH: Fas ligand mediates activation-induced cell death in human T lymphocytes. J Exp Med 1995;181:71–77.
42 Watanabe-Fukunaga R, Brannan CI, Copeland NG, Jenkins NA, Nagata S: Lymphoproliferation disorder in mice explained by defects in Fas antigen that mediates apoptosis. Nature 1992;356:314–317.
43 Boldin MP, Varfolomeev EE, Pancer Z, Mett IL, Camonis JH, Wallach D: A novel protein that interacts with the death domain of Fas/APO1 contains a sequence motif related to the death domain. J Biol Chem 1995;270:7795–7798.
44 Thornberry NA, Bull HG, Calaycay JR, Chapman KT, Howard AD, Kostura MJ, Miller DK, Molineaux SM, Weidner JR, Aunins J, et al.: A novel heterodimeric cysteine protease is required for interleukin-1 beta processing in monocytes. Nature 1992;356:768–774.
45 Cerretti DP, Kozlosky CJ, Mosley B, Nelson N, van Ness K, Greenstreet TA, March CJ, Kronheim SR, Druck T, Cannizzaro LA, et al.: Molecular cloning of the interleukin-1 beta converting enzyme. Science 1992;256:97–100.
46 Enari M, Hug H, Nagata S: Involvement of an ICE-like protease in Fas-mediated apoptosis. Nature 1995;375:78–81.
47 Rothe M, Pan MG, Henzel WJ, Ayres TM, Goeddel DV: The TNFR2-TRAF signaling complex contains two novel proteins related to baculoviral inhibitor of apoptosis proteins. Cell 1995;83:1243–1252.
48 Whitten JM: Cell death during early morphogenesis: parallels between insect limb and vertebrate limb development. Science 1969;163:1456–1457.
49 Yuan J, Shaham S, Ledoux S, Ellis HM, Horvitz HR: The C. elegans cell death gene ced-3 encodes a protein similar to mammalian interleukin-1 beta-converting enzyme. Cell 1993;75:641–652.
50 Chiou SK, Rao L, White E: Bcl-2 blocks p53-dependent apoptosis. Mol Cell Biol 1994;14:2556–2563; erratum in: Mol Cell Biol 1994;14:4333.
51 Danilevicius Z: Apoptosis: a factor in neoplastic growth? JAMA 1973;223:434–435.
52 Clouston WM, Kerr JF: Apoptosis, lymphocytoxicity and the containment of viral infections. Med Hypoth 1985;18:399–404.
53 Strasser A, Whittingham S, Vaux DL, Bath ML, Adams JM, Cory S, Harris AW: Enforced BCL2 expression in B-lymphoid cells prolongs antibody responses and elicits autoimmune disease. Proc Natl Acad Sci USA 1991;88:8661–8665.
54 Roy N, Mahadevan MS, McLean M, Shutler G, Yaraghi Z, Farahani R, Baird S, Besner-Johnston A, Lefebvre C, Kang X, et al.: The gene for neuronal apoptosis inhibitory protein is partially deleted in individuals with spinal muscular atrophy. Cell 1995;80:167–178.
55 Elmore S: Apoptosis: a review of programmed cell death. Toxicol Pathol 2007;35:495–516.
56 Li B, Ju W, Zhang C, et al.: Growth arrest and apoptosis of the human hepatocellular carcinoma cell line Bel-7402 induced by melittin. Onkologie 2006;29:367–371.
57 Ehlert JE, Kubbutat MHG: Apoptosis and its relevance in cancer therapy. Onkologie 2001;24:433–440.