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The role of apoptosis in aging and age-related disease: update

Neue Befunde zur Funktion der Apoptose im Rahmen der Alterung und bei alterns-assoziierter Krankheit

Summary Programmed death of cells by apoptosis is regarded as a protective mechanism of the organism against an accumulation and spread of defective cells. The rate of apoptosis is elevated in most types of aging cell populations. However, there are also findings about a decreased susceptibility of senescent cells in vivo and in vitro, particularly to apoptosis induced by oxidative and energetic stress. Mitochondria appear to have a key function in apoptosis regulation. Thus, apoptosis can be induced by defective mitochondrial oxidative phosphorylation. The role of apoptosis in aging and age-related disease was outlined for different organs (brain, cardio-vascular system, immune system, intestine, macula of the eye, Langerhans islets, prostate gland, oocytes of ovaries). The age-related intensification of this dismantling system of cells seems to highlight the deterioration of tissue and organ structure and function in aging.

Key words Apoptosis – aging – age-related disease

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Zusammenfassung Der programmierte Zelltod durch Apoptose wird als Schutzmechanismus des Organismus gegen Anhäufung und Ausbreitung von geschädigten Zellen gedeutet. Die Apoptoserate ist in den meisten alternden Zellpopulationen erhöht. Jedoch gibt es auch Befunde über eine verminderte Anfälligkeit von seneszenten Zellen in vivo und in vitro gegen Apoptose, die insbesondere durch oxidativen oder energetischen Stress hervorgerufen wird. Mitochondrien haben offenbar eine entscheidende Funktion bei der Apoptoseregulation. So kann Apoptose durch eine defekte mitochondriale oxidative Phosphorylierung induziert werden. Für verschiedene Organe wurde ein Überblick zur Rolle von Apoptose im Rahmen der Alterung bzw. von alterns-assoziierter Krankheit gegeben, und zwar für Gehirn, Herz-Kreislauf-System, Immunsystem, Darm, Makula des Auges, Langerhans-Inseln, Prostata und Oozyten von Ovarien.

Die alterns-assoziierte Intensivierung dieses Demontagesystems von Zellen markiert offenbar die im Alternsgang auftretende Verschlechterung von Struktur und Funktion von Geweben und Organen.

Schlüsselwörter Apoptose – Altern – Alterskrankheiten

Introduction

Apoptosis is an evolutionary well-shaped and widespread mechanism. Analysis of the programmed death phenomena at various levels of biological organization, i.e., mitochondria (mitoptosis), cells (apoptosis), organs (organoptosis) and organisms (phenoptosis) may support Weismann's concept that removal of unwanted or damaged elements could be essential for the biological communities due to prevention of appearance of asocial monsters capable ruining the kin and entire community (36). Altruistic programmed cell death may serve useful functions not only in multicellular organisms but also in protozoan and eukaryotic unicellulars, e.g., limiting the spread of viral infection or donating nutrients to kin cells. Apoptosis-like elimination of old or defective cells was shown to be common in eukayotic yeast which used terminal sporulation factors and autolysins for the old mother cells' self-destruction. However, programmed death mechanisms should be absent in „persistors", rare cells that are resistant to self-killing to ensure population survival (22).

Age-associated changes of the genes involved in apoptosis could be among the most prominent alterations of gene expression in aging. For instance, the genome-wide microarray expression analysis of 11 000 genes in the aging mice liver allowed the conclusion that aging was associated with alteration of genes involved in decreased capacity for apoptosis, cell-cycling, DNA replication and xenobiotic metabolism and elevated inflammation, cellular stress, and fibrosis. Caloric restriction reversed majority of these alterations. Even short-term (4 weeks) caloric restriction shifted the „normo-aging" genomic profile of old control mice toward the „slow-aging" profile characteristic for the chronically restricted animals (4).

Modulation of p53 and downstream p21 are pivotal in regulation of apoptosis. p21 up-regulates multiple genes associated with senescence and age-related diseases, including atherosclerosis, Alzheimer's disease, amyloidosis, arthritis, etc. Induction of p21 triggers cyclin-dependent kinases' inhibition and cell growth arrest, whereas overexpression of p21 induces phenotypic features of senescence. cDNA array hybridization revealed that p21 expression selectively inhibited a set of genes involved in mitosis, DNA repair, replication, and segregation. Reexpression of these genes causes reentry of cells into the cell cycle (5).

Mitochondria

Mitochondria are known as key factors of apoptosis regulation in aging. In cardiac muscle, CNS, kidney or neurohumoral tissues, defective mitochondrial oxidative phosphorylation caused by impaired electron transport chain enzymes or lack of electron carrier coenzyme Q10 may result in insufficient mitochondrial membrane potential and opening of the mitochondrial membrane pores, culminated by activation of apoptosis (9). In embryos with homozygous disruption of the mitochondrial transcription factor A gene (Tfam), severe respiratory chain deficiency in the heart was associated with massive apoptosis. Furthermore, mitochondrial (mt) DNA-less cell lines were also highly susceptible to apoptotic stimuli (41). The rates of DNA fragmentation and apoptotic neuronal death in the striatum of old mice were higher in response to oxidative stress induced by a mitochondrial toxin, 3-nitropropionic acid, whereas the activation of DNA repair enzymes was attenuated (18). However, apoptosis regulation can involve a variety of „unexpected players", telomeres included. For instance, telomerase activity and its essential catalytic subunit, telomere reverse transcriptase (TERT), are expressed in neurons of embryonic and early postnatal brains and are down-regulated afterwards. Suppression of TERT expression in cultured embryonic hippocampal neurons increased their excitotoxicity and apoptosis, whereas TERT overexpression suppressed apoptosis induced by trophic factors withdrawal. TERT may be a survival-promoting factor, exerting its anti-apoptotic effect at early stages of a cell's programmed death, prior to mitochondrial dysfunction and caspases activation (10).

During the last few years, apoptosis has been intensively studied in the aging nervous, immune, cardiovascular, endocrine, reproductive system, and some other organs. The results of the relevant studies are briefly described below.

Brain

Excitatory glutamate-induced apoptosis may play an important role in neurological diseases of aging. Exposure of cerebellar granule cell cultures to glutamate-induced apoptosis which was associated with activation of NF-kappaB and p53, as well as p53-downstream genes p21, which inhibits different cyclin-dependent kinases, and MSH2, which is involved in recognition and repair of DNA mismatches. Pretreatment of the cultures with aspirin, which inhibits NF-kappaB, or with specific p53 antisense oligonucleotide, which inhibits p53 transcription, resulted in

complete prevention of glutamate-induced p53 activation and apoptosis (39). In general, p53-associated apoptosis may be a common mechanism in neuronal loss in the aging brain and age-related degenerative diseases. Immunoreactive p53 was found in the hippocampus, septal region and cerebellum of aged but not adult rats. Up-regulation of p53 in the Purkinje cells may explain heavy losses of these cells in aging (6).

Expression of Bcl-2 is up-regulated in the hippocampus and cerebellum of intact aged (24 months) Fischer 344 rats. In the group of young rats (3 months), the Bcl-2 up-regulation occurred after exposure to 100% O_2 for 48 hours. Treatment with free radical spin traps efficiently reversed the age-associated Bcl-2 up-regulation, suggesting the role of redox status in Bcl-2 expression (17) .

Up-regulation of neurotrophic factors can protect against excessive apoptotic cell losses induced by neurohumoral perturbations. In the dentate gyrus of Fischer rats ranging from 2 to 26 months of age, adrenalectomy increased the number of apoptotic cells, compared with sham-operated or corticosterone-treated animals. In granule cells of the hippocampus, glucocorticoid receptor activation increased apoptosis, whereas mineralocorticoid receptor activation rendered neuroprotective effects. The opposing effects of gluco- and mineralocorticoids on neuronal survival could be explained by their ability to differentially activate pro- and antiapoptotic genes. In contrast to mineralocorticoids, glucocorticoids increased the ratio of Bax to Bcl-2 or Bcl-xl and activated p53. Although the same type shifts were observed for both young and old animals, old subjects were more susceptible to the glucocorticoid-mediated apoptosis (1).

Rasagiline and structurally related (–)deprenyl or propargylamines could be used as neuroprotective agents in aging and age-related neurodegenerative diseases, rescuing neurons from the activated mitochondrial apoptotic cascade. At chronic administration, rasagiline increased superoxide dismutase and catalase activities and protected cells from neurotoxin- or oxidative stress-induced apoptosis (26). Rasagiline protected dopaminergic neurons from apoptosis due to stabilization of the mitochondrial membrane potential, prevention of oxidative stress, DNA fragmentation, and activation of caspase 3. The opening of permeability transition pores was prevented even in isolated mitochondria (27).

Cardio-vascular system

There is increasing evidence of a relationship between apoptosis and cardiovascular diseases, particularly for the most frequent heart diseases in elderly populations – ischemic heart disease and congestive heart failure. It is assumed that prevention of apoptosis may decrease the incidence of cardiac failure and elevate the survival of endothelial and smooth muscle cells in the elderly (8).

When human vascular endothelial cells have been serially passaged and aged in vitro, immunohistochemical visualization of the growth fraction by antisera to the proliferation marker pKi67 showed a 4.4% decline per population doubling without a significant change of the cell cycle time. The number of senescent cells assessed by beta-galactosidase activity increased by 6.5% for each population doubling, significantly exceeding the 0.3% increase of apoptosis and suggesting rapid accumulation of senescent cells in aging vascular endothelium (16).

Young (7 years) and old (20 years) *Macaca fascicularis* were chronically instrumented for measurement of the left ventricular and aortic pressures and cardiac output. There was no evidence of atherosclerosis. Moreover, no age-differences were found for total cholesterol, triglyceride, fasting blood sugar, baseline aortic pressure and total peripheral resistance. However, the rate of apoptosis was higher in the old monkeys' endothelial cells and correlated with reduced density of endothelial cells in the femoral arteries and depressed responses to acetylcholine (2).

In the heart of spontaneously hypertensive rats (SHR), a significant increase of apoptosis began as early as at 4 weeks of age and maintained high levels throughout aging. The blood pressure increase preceded the activation of apoptosis, registered starting from the 5^{th} week. The ratio Bax/Bcl-2, apoptosis rate and fibroblast content were significantly elevated in SHR, compared with normotensive animals of the same strain. Ramipril, a caspase inhibitor, effectively reduced the Bax/Bcl-2 ratio and apoptosis rate in SHR (23).

Immune system

Apoptosis is vital in controlling cell number, deleting self-reactive cells and maintaining immune surveillance in aging. Natural killer (NK) cells are a critical first barrier against viral infection and tumor development. In adult (6 months) C57BL/6J mice, NK activity was higher in both in vivo or in vitro stimulation by interferon IFN-α/β, compared with old (24 months) animals. Flow cytometry revealed that IFN-α/β binding was comparable in young and old animals. However, Fas (CD95) expression and Fas-activated cell death were higher in the old NK cells, suggesting an apoptosis role in the declined NK-cytotoxicity in aging (31).

Comparison of the lymphocytes derived from young and old humans showed increased sensitivity of both CD4+ and CD8+ cell subsets to TNF- and Fas-mediated apoptosis. The higher sensitivity was associated with overexpression of the death receptor and adapter molecules, involved in cell death signaling. The expression of initiator caspase 8 and effector caspase 3 was also increased in these cells. Moreover, the expression of both mRNA and protein of Bax was increased and Bcl-2 decreased in the lymphocytes taken from elderly, suggesting the key role of apoptosis in age-related lymphopenia and T cell deficiency (13).

In spontaneous and activation-induced models, the peripheral blood lymphocytes of elderly (over 60 years) showed higher rates of apoptotic cell accumulation, compared with younger (less than 35 years) individuals. Expression of Bcl-2 was increased in aging and correlated with the number of apoptotic cells. Treatment with oxidative stressor 2-deoxy-D-ribose aggravated the age-changes of the lymphocytes' apoptosis (35).

Using biopsy samples of the bone marrow obtained from newborn to 100 year old patients, it was shown that the cellularity did not change significantly with age up to 80 years but decreased in the oldest (80–100 years). The age-dynamics of cellularity was supported by opposite age-changes of proliferative capacity and apoptosis in the oldest group where the rate of apoptosis was significantly increased, whereas proliferative capacity was decreased. The percentage of T and B cells showed a peak at the sixth decade with a gradual decline thereafter. In general, the data suggest that hypocellularity in the bone marrow of the elderly could be explained by higher rates of apoptosis, leading to decreased number of lymphocytes and macrophages in aging (30).

The rate of UVC-induced apoptosis, as assessed by morphological changes, DNA fragmentation, and Bcl-2 and Bax expression, in the culture of splenocytes derived from young (3 months) rats was twice lower, compared with old (24 months) animals (20% versus 40%). Apoptosis in the splenocytes from old rats often did not exhibit symptoms typical for programmed death, such as DNA fragmentation or Bcl-2 down-regulation (33).

Endocrine system

Apoptosis is assumed to play an important role in the manifestation of insulin-dependent and insulin-independent diabetes mellitus. The study of pro- and antiapoptotic peptides (Bak, Bax, Fas, Fas-ligand, and Bcl-2) during the pre- and postnatal ontogenesis revealed biphasic apoptotic activity in the Langerhans islets of rats. The first peak appeared at the fifth day of postnatal life. The second phase began at the age of 1 month and peaked at 18 months (14).

Growth, differentiation, and death of the prostate gland cells is androgen dependent. However, in aging these cells develop androgen independence, and their survival does not require androgens, leading to the hypertrophy of dorsal and lateral lobes of the prostate. Castration of young (4 months) and old (24 months) rats induced apoptosis and tissue mass loss. The rate of apoptosis was lower in all lobes of the old prostate. The lower rates of apoptosis in the dorsal and lateral lobes of prostate contribute to the lobe-specific overgrowth of the old prostate (3). Pharmacological intervention could be quite rewarding in treatment of the age-related prostate hypertrophy. In vitro effects of α-adrenoreceptor antagonists terazosin and doxazosin have been examined as inhibitors of proliferation and inducers of apoptosis in benign and malignant prostate tumor growth. The drugs suppressed prostate growth due to inducing apoptosis in a dose-dependent manner without an effect on proliferation (19).

Intestine

Due to specific spatial and hierarchical organization, the intestinal epithelium is an excellent model to study stem cells. The intestinal stem cells are located at the 4^{th}–5^{th} cells' position from the bottom of the crypt and can be studied together with their daughter cells, as they divide, differentiate and migrate along the crypt-villus axis. Stem cells may have a pivotal role in aging since any senescent decline in them will impair the capacity of renewal and turnover of the committed differentiated cells. The study of the stem cells' ability to undergo apoptosis and regenerate the epithelium after injury revealed that the stem cells of old mice showed elevated levels of apoptosis and fewer surviving crypts following exposure to ionizing radiation. In the crypts of old animals, there was a growth delay despite the higher number of cells susceptible to regeneration. Age-associated alterations in the level of p53 and p21 expression suggested defects in recognition of damage and initiation of apoptosis or repair of the damaged cells (32).

The study of age-associated alterations in mRNA and protein expression of genes involved in regulation of proliferation and apoptosis in the colonic epithelium of Fischer 344 rats exhibited significantly higher expression of Bax in aging. The Bax expression was especially high in the upper part of a crypt. No significant changes were found for p53 and proliferation,

suggesting the elevated levels of Bax as a factor promoting apoptosis in the aging colonic cripts (21).

Western-style diets are capable of triggering and developing dysplastic crypts and early stages of tumorogenesis in the colon. During the second half of a rodents' life span, feeding of Western-style diets resulted in activation of apoptosis at the base but not in the upper third of the crypt or in the surface epithelium (34).

Reproductive system

The majority of human oocytes present in fetal ovaries are depleted by apoptosis before birth, and only 400 will ovulate during the fertile period of life. In fact apoptosis and expression of Bcl-2 and Bax were preserved throughout fetal and adult ovarian follicles (40). Apoptotic alterations could be a reason for lower fertility in old women. In three age-groups (20–31 years, 31–40 years, and 41–50 years) of healthy women, apoptosis was registered in 17%, 38%, and 52% of oocytes, respectively. Incubation of human oocytes for 32–120 hours resulted in maturation and apoptosis. The rate of maturation was the highest in the young age-group and the lowest in the old age-group. In contrast, the rate of apoptosis was lower in oocytes taken from younger women. Apoptotic oocytes exhibited typical morphology of programmed cell death, including cell shrinkage, cytoplasm condensation, DNA fragmentation, membrane blebbing, and cell fragmentation into apoptotic bodies (43).

However, donation of oocytes from younger to middle-aged women abrogated the effect of aging on fertility, suggesting that oocytes could be the major cause of reproductive aging. The results of experiments with mouse zygotes suggested that cytoplasm, and most likely mitochondria, may play a central role in developmental and oxidative stress-induced apoptosis in the zygotes (24). In fact oxidative stress may have fatal consequences for a zygote's development. Shortly after treatment with 1 mM hydrogen peroxide for 90 min, mouse fertilized oocytes displayed changes typical for apoptosis, including cell shrinkage, cytochrome c release from mitochondria, condensed pronuclei, and caspase activation (25).

Eye

Macular degradation is the leading cause of severe visual impairment in aging humans. In macular degradation, retinal pigment epithelial cells accumulate lipofuscin and die by apoptosis with subsequent death of photoreceptor cells. The apoptosis was preceded by appearance of pro-apoptotic cytochrome c and apoptosis inducing factor in the cytoplasm and nucleus (38). Apoptosis could be the main cause of photoreceptor cell death in variety of other types of retinal degradation in humans and primates. In maculae of rhesus monkeys, aged 6-34 years, the TUNEL method revealed apoptotic cells at all ages. However, the number of apoptotic cells was higher in the oldest animals (20).

Conclusion

Apoptotic losses have been found to be increased in most types of aging cell populations (see also: 29). However, there are also reports about a reduced responsiveness of senescent cells in vivo and in vitro, particularly to apoptosis induced by oxidative or energetic stress (11, 28, 37, 42). Although apoptosis is regarded as a protective mechanism of the organism against an accumulation and spread of defective cells, the preponderance of this dismantling system seems to highlight the age-associated decline and deterioration in tissue and organ structure and function.

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