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APOPTOSIS AND ITS ROLE IN AGEING: AN OVERVIEW

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ABSTRACT

Apoptosis is a programmed form of cell death, which primarily functions to eliminate altered cells that are useless or harmful for multicellular organisms. Molecular mechanisms of apoptosis include two major pathways: intrinsic and extrinsic, involving a number of molecules and organelles. Various genes and their products play a central role in control of apoptosis through promotion or inhibition of apoptotic pathways. Dysregulation of the apoptotic process may be related to aging process. The possibility that apoptosis participates in the ageing opens several novel opportunities to manipulate age related changes by regulating the apoptotic process.

INTRODUCTION

The death of cells in tissues of humans and other multicellular organism is neither always abnormal nor always detrimental. Although necrosis ensues at the site of massive cellular injury, most cells in the body die through a more subtle, non inflammatory energy dependent form of cell death called apoptosis [1]. Apoptosis occurs normally during development and aging and as a homeostatic mechanism to maintain cell populations in tissues. Apoptosis also occurs as a defense mechanism such as in immune reactions or when cells are damaged by disease or noxious agents [2].

Historical background: The very first cells described by Hooke in 1665 from cork were named 'Cells'. These cells were found to be corpses that had died physiologically. That cell death occurs in a predictable programmed fashion in physiological circumstances was first recognized by Carl Vogt (1842), who saw dying cells in the neural system of developing toad embryos. Lokshin coined the phrase 'Programmed cell death' in 1965 to describe cell death in insect metamorphosis [3].

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Kerr, Wyllie and Currie, 1972 discovered a mode of cellular death with ultra structural features consistent with an active, inherently controlled phenomenon, playing an important role in the regulation of cell numbers in a variety of tissues under both physiological and pathological conditions. Because of its important kinetic significance, they called it 'Apoptosis'. The word apoptosis was suggested by Prof. James Cormack, University of Aberdeen [4].

Other types of cell death

Cell death can be controlled or uncontrolled. (Fig. I)

Necrosis is the pathologic cell death resulting from external or internal stimuli occurring in acute, non-physiological injury. Until the 1970's, necrosis was the only clearly identified type of cell death, thus making cell death seem a non-physiological and detrimental event [1]. (Table I).

Autophagic cell death is a dynamic process in which sub cellular membranes undergo dramatic morphological changes [5]. Apoptosis and autophagic cell death differ in several ways (Table II).

The morphology of apoptosis

Electron microscopy shows that the structural changes in apoptosis take place in two discrete stages:

1. Formation of apoptotic bodies
2. Their phagocytosis and degradation by other cells.

The formation of apoptotic bodies involves marked condensation of the nucleus and cytoplasm, nuclear fragmentation and separation of the protuberances that form on the cell surface to produce many membrane-bound, compact, but otherwise well preserved cell remnants of greatly varying size. The contents of an apoptotic body depend on the cellular constituents that happen to be present in the cytoplasmic protuberance that give rise to it; small apoptotic bodies thus occasionally consist almost entirely of condensed nuclear chromatin, whereas others are composed of only cytoplasmic elements (Fig. II). The condensation is presumably a consequence of the extrusion of water. Subsequent to their ingestion by other cells apoptotic bodies undergo a process within phagosome that is ultra structurally very similar to ischemic coagulative necrosis. The matrix of mitochondria becomes electron lucent and displays focal flocculant densities, and ribosomes become swollen and indistinct. It should be noted that this is the first stage at which the bodies exhibit changes that indicate cessation of co-ordinated metabolic activity. It is difficult to determine precisely the time taken for the sequence of events described; however, examination of the serial changes that take place in several experimental models suggests that the process is completed fairly rapidly: bodies may form and disappear within 24 hrs [5].

Apoptotic pathways of cell death

I Caspase dependent pathway

1. Death receptor dependent (extrinsic)
2. Mitochondria dependent (intrinsic)

Extrinsic pathway It involves activation of specific cell membrane receptors, which belong to tumor necrosis factor receptor (TNF) family and are collectively known as death receptors including, TNF receptor1, Fas, DR3, DR4, DR5, DR6. Upon binding to specific ligands, such as TNFα, lymphotoxin, Fas ligand, Apo3 ligand and TRAIL, these receptors undergo conformational changes that allow them to interact with specialized intracellular adaptor proteins. Formation of these complexes initiates the cascade of caspase activation, which terminates with the apoptotic death of the cell [6].

Intrinsic pathway It is mediated by Bax/Bak and involves the release of cytochrome c. In general, Bax is associated with 14-3-3 protein, which anchors Bax in the cytoplasm. Homodimerization of Bax, or Heterodimerization of Bax and Bak, results in translocation of Bax from the cytoplasm to mitochondria. Bax homodimers and heterodimers interact with a voltage dependent anion channel (VDAC) in the mitochondrial outer membrane to release cytochrome c by increasing mitochondrial membrane permeability (MMP) via opening of the mitochondrial permeability transition pore. The release of cytochrome c results in the formation of an apoptosome, consisting of apoptosis activating factor 1 and procaspase 9, after which dATP activates caspase 9, leading to apoptosis.

II Caspase independent pathway Apoptosis inducing factor (AIF) is a phylogenetically conserved flavoprotein within the mitochondrial membrane, which has the ability to induce apoptosis via a caspase independent pathway. AIF induces nuclear chromatin condensation and large scale DNA fragmentation, and is essential for programmed cell death. On lethal signaling, AIF translocates through the cytosol to the nucleus where it binds to DNA and provokes caspase independent chromatin condensation [7].

Apoptosis in ageing It is usually defined as the progressive loss of function accompanied by decreasing fertility and increasing mortality with advancing age [8].

Theories

There are several theories of ageing and fall into two general categories:

1. The stochastic model of ageing
2. Programmed model of ageing- regulation of specific genes

Stochastic model- Suggest that damage to cells and molecules underlie ageing. DNA damage and damage to proteins from a variety of sources, with emphasis on free radicals and glycation, combine to produce manifestations of ageing. Random environmental events such as oxygen free radical damage, somatic cell gene mutation, or cross linkage among macromolecules, particularly proteins, alter the DNA's ability to function normally.

Collagen cross linking- With age, collagen becomes soluble, rigid and cross linked. Free radicals, glucose and UV light are thought to increase collagen cross linking. Functionally, the age related changes in collagen are observed in skin, loosened teeth, clouded lens, reduced kidney function, damaged lungs, reduced muscle capacity, reduced joint mobility and altered circulatory effects.

Free radical theory- The free radical theory suggests that products of oxidation metabolism can react with key cellular constituents, including proteins, DNA and lipids, to generate long lived dysfunctional molecules that interfere with cellular function. The most vulnerable biological structure damaged by free radical is plasma membrane. Damage to mitochondrial DNA results in body's inability to produce adequate energy for increased activity level and may have a significant impact on skeletal muscle strength. Free radical damage alters essential organ function.

Table 1. Differences between necrosis and apoptosis

Features	Necrosis	Apoptosis
Stimuli	Toxins, severe hypoxia, Massive insult, conditions with ATP depletion.	Physiologic and pathologic conditions without ATP depletion.
Energy requirement	None	ATP dependent
Histology	Cellular swelling, disruption of organelles, death of patches of tissue.	Chromatin condensation, apoptotic bodies, death of single isolated cells.
Plasma membrane	Lysed	Intact, blebbed with molecular alterations.
DNA breakdown pattern	Randomly sized fragments.	Ladder of fragments in inter nucleosomal multiples of 185 base pairs.
Phagocytosis of dead cells	Immigrant phagocytosis.	Neighboring cells.
Tissue reaction	Inflammation	No inflammation.

Table 2. Comparison of characteristics between Apoptosis and Autophagy

Factor	Apoptosis	Autophagy
Nucleus	Chromatin condensation, DNA laddering and fragmentation , pyknosis	Partial chromatin condensation, No DNA laddering and frag- mentation , sometimes pyknosis
Cytoplasm	Cytoplasmic condensation Fragmentation of apoptotic bodies Increase in MMP Activation of Caspase cascade Potential release of lysosomal enzymes	Many large autophagic vacuoles Many autophagosomes Potential involvement of MMP Caspase independent Lysosomal activation
Membrane	Blebbing	Blebbing
Primary protease	Caspase such as caspase 3	Cathepsin and Proteosomal proteins
ATP requirement	Yes	Yes
Inhibition	z- VAD- fmk, XIAP, Bcl-2/ Bcl-XL, Sometimes actinomycin D, Sometimes cyclophosphamide	3-methyl adenine, P13 K inhibitors, P13 K-1/ Akt, Actinomycin D, Cyclophosphamide
Detection	DNA laddering test, Caspase activation, TUNEL and annexin V staining, Electron microscopy	Lysosome activity test, Cytoplasmic sequestration test, LC3 associated with autophagosome membrane, Electron microscopy
MMP – mitochondrial membrane permeability XIAP- X chromosome encoded inhibitors of apoptosis proteins PI 3 K- Phosphoinositide 3 kinase TUNEL- terminal deoxynucleotidyl transferase nick end labeling FACS- fluorescence activated cell sorting AMPK- AMP activated protein kinase.		

Glycosylation theory- Non enzymatic glycosylation can create modified forms of proteins and perhaps other macromolecules that accumulate and cause dysfunction in ageing. Glucose joins with certain amino acids in proteins, rendering an altered amino acid, and ultimately a dysfunctional protein. The glycosylated proteins are damaged and termed as advanced glycation end products. Adverse effects from glycation include body stiffing, reduced ability to control body vessel linings, increased blood clotting, eye damage.

Pre programmed gene regulation The regulation of specific genes proposes that the ageing process is actively programmed by the cell's genetic machinery. This category of ageing theories maintains that ageing occurs because of apoptosis induced by endogenous ligand Fas, and this intrinsic timing mechanisms and signals [9].

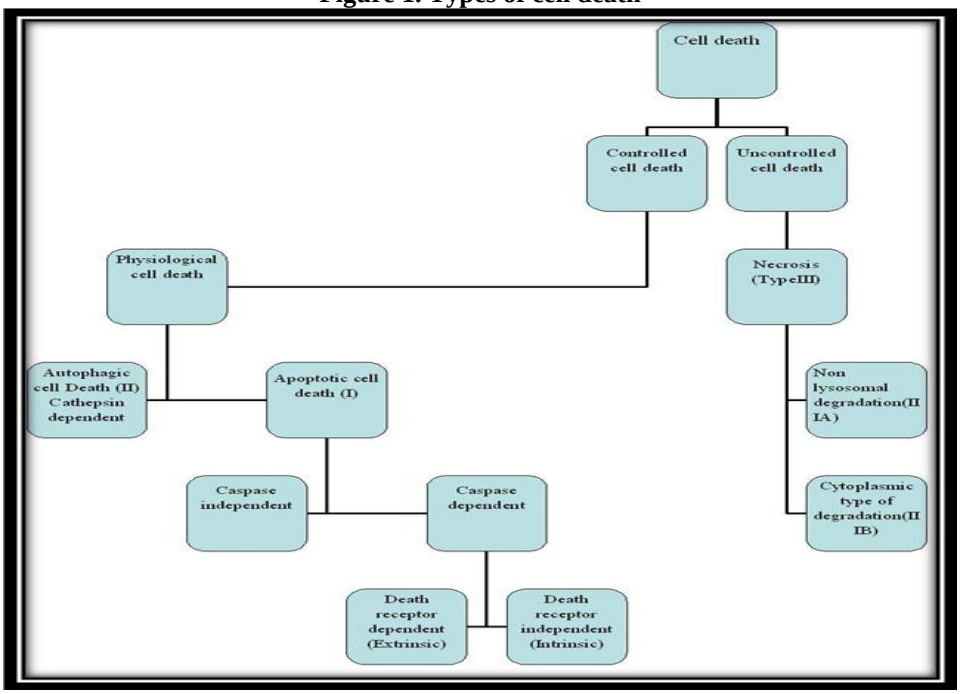
Effect of apoptosis on aging A generalized defect in the control of apoptosis has been proposed to cause or contribute to ageing. One might imagine two scenarios by which the cellular process of apoptosis might be interconnected with the intrinsic process of ageing. First an upstream, fundamental mechanism of ageing might alter the control of apoptosis, which, in turn, would lead to ageing phenotypes and age related diseases. One or more basic ageing process might alter the regulation of apoptotic response, at least in certain cell types. Ageing appears to suppress the apoptotic response, and the suppression is retarded by regimes (caloric restriction) that retard ageing. Ageing has been reported to sensitize hepatocytes to sensitization is reversed by caloric restriction. Findings

suggest that one or more fundamental processes, that are responsible for ageing, may alter the regulation of apoptosis. Second, it is possible that normal apoptotic responses and their regulation might lead directly to aging phenotypes and /or age related pathology [10]. An increased interest in the study of aging has been stimulated by lengthening life span and percentage of elderly population [11].

Mechanisms underlying age enhanced apoptosis In non dividing cells and stable cells, age is associated with a significant enhancement of apoptosis under physiological conditions and/or susceptibility to cell death after challenges. Several recent studies have suggested that Fas ligand / receptor signaling seems to be the major signal pathway in age enhanced apoptosis. It has been demonstrated that activation of p53 mediated transcription is a critical cellular response to oxidative stress and DNA damage. Findings suggest that, apoptosis induced by oxidative stress or DNA damage is mediated, at least in part, by p53 dependent activation of Fas ligand/ receptor system [12].

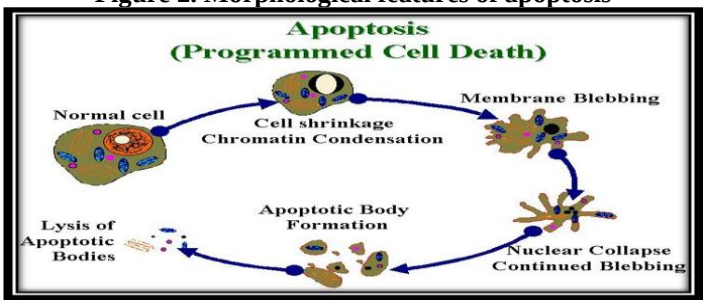
Clinical implications Abnormalities in the regulation of apoptosis may contribute to the pathogenesis of a variety of disorders. Aging is associated with increase in frequency of infection and increased incidence of cancer. Increased apoptosis of both $CD4^+$ and $CD8^+$ in aging may contribute to both increased frequency of infection and increased incidence of cancer. Increased apoptosis of both $CD4^+$ and $CD8^+$ T cells has also been observed in AIDS, which, similar to aging, is also associated with T cell deficiency, increased frequency of infections, and increased incidence of malignancies [13].

Figure 1. Types of cell death



Courtesy: R. Sensenig, S. Kalghatgi, E. Cerchar. (2011). Non-Thermal Plasma Induces Apoptosis in Melanoma Cells via Production of Intracellular Reactive Oxygen Species. Brooks, Annals of Biomedical Engineering, 39 (2), 674 – 687.

Figure 2. Morphological features of apoptosis



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CONCLUSION

Apoptosis is the guardian of tissue integrity by removing unfit and injured cells without evoking inflammation. During aging accumulated cell damage and altered signaling can cause too little or too much cell death thereby limiting tissue function. For these reasons apoptotic pathways are the promising targets for interventions in aging and age related changes. Apoptosis regulates various processes of body including aging. Manipulating the apoptotic pathways can be helpful to regulate the changes seen in the aging and to improve overall functioning.

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