Review Article

APOPTOSIS AT A GLANCE: DEATH OR LIFE?

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ABSTRACT

Apoptosis or programmed cell death that is genetically regulated is a process for killing cells. It is essential for the normal function of organisms and therefore variety of diseases including autoimmunity and cancer result from any defect in this physiological process. Two pathways are responsible for signalling apoptosis: intrinsic or mitochondrial pathway and extrinsic or death receptor pathway. As a final result of this process, cell destruction activated by a family of cysteine proteases (caspases) takes place. This article summarizes current knowledge of apoptosis.

KEY WORDS: Apoptosis, Caspases, Mitochondria.

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INTRODUCTION

Apoptosis was first described by the Australian pathologist; John Kerr in 1965. He recognized a distinct form of cell death and named it "shrinkage necrosis". In 1972 the term apoptosis was introduced by John Kerr, Alastair Currie and Andrew Wyllie for what was now recognized as a morphologically typical, dynamically controlled form of cell death.[1] The term apoptosis was suggested by James Cormac, professor of classical Greek at the University of Aberdeen and is derived from the Greek meaning "dropping off" and so signifies the dropping of leaves from the tree.[2] Apoptosis or programmed cell suicide is a genetically regulated, active process that eliminates cells in both physiological and pathological processes. It is characterized by profound and distinct changes in cellular architecture leading to self destruction.[3,4] It is a normal physiological response to specific suicide signals, or lack of survival signals. It has an essential role in shaping tissues during development, endocrine dependent atrophy and normal cell turnover in many tissues.[5] It also limits the accumulation of harmful cells, such as self-reactive lymphocytes, virus-infected cells and tumour cells.[6]

Significant progress has been made in defining the mechanisms of apoptotic control underlying the pathophysiology of viral infections, autoimmune diseases, neurodegenerative disorders, immunologic deficiencies, and cancers. In fact apoptosis itself plays a key role in the development of the immune system, controlling the immune response; deleting immune cells recognizing self-antigens, and cytotoxic killing.

Defects in the regulation of apoptosis in the immune system may lead to autoimmune disease.[7] In many virus-infected cells, virus replication will kill the cell, releasing virus particles. Since the cell is doomed anyway, it is in the host's interest to destroy the infected cell sooner rather than later and thus prevent or minimize virus replication. In an immune individual this may be accomplished by the active immune response generating cytotoxic T cells or antibody dependent cell killing. However, apoptosis may be seen as an innate equivalent

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of this process that may well have predated the development of the more active immunological mechanisms in evolutionary terms.

Typically apoptotic cell death proceeds morphologically with several characteristic features such as chromatin margination and nuclear fragmentation. Several endonucleases such as Caspase-activated DNAse (CAD), lysosomal DNAse II have been found responsible for DNA fragmentation in apoptotic cells.[8] Apoptotic cells shrink and finally give rise to the formation of apoptotic bodies, which are small membrane-bound blebs containing the cell's contents.[9,10] The apoptotic bodies are taken up by macrophages and degraded. This avoids the release of soluble cell contents that would otherwise lead to inflammation. The apoptotic process can therefore be divided into three morphological phases: phase one includes changes such as cell shrinkage and extensive chromatin condensation. Phase two includes formation of vacuoles inside the cells and cell fragmentation; phase three includes formation of apoptotic bodies.[11]

It is important to distinguish between necrosis and apoptosis; Necrosis is considered to be a passive event that is largely dependent on the type of the external injurious agent. After necrosis there are many changes in the cell structure. The most important changes are: clumping of the chromatin, swelling/rupture of mitochondria and lysis of the plasma membrane. Cell contents spill out and a general inflammatory response is triggered. In contrast, the outer membrane of the cell remains intact in apoptosis and no inflammatory reaction is provoked, leaving the neighboring cells and tissues unharmed. Moreover, the distinct morphological features in apoptosis, i.e. chromatin margination, nuclear fragmentation, cellular shrinking and formation of apoptotic bodies do not take place in necrosis.[12] Intracellular ATP levels have been implicated as an important factor in the cell's decision to die by apoptosis or necrosis; apoptosis is ATP-dependent but necrosis is associated with depletion of intracellular ATP indicating that this process does not require ATP.[13-17] There is accumulating evidence that apoptosis and necrosis are related phenomena[18] and in tumours, increased numbers of apoptotic cells are seen adjacent to necrotic areas.[19]

A family of cysteine proteases (called caspases), which are present in most cells are responsible for apoptosis. Several members of this family have been identified and these are termed caspase-1 to caspase-14.[20] The first known protease of the caspase family is interleukin-1 b-converting enzyme (ICE, caspase-1).[21] They are themselves activated by specific proteolytic cleavage and then cleave their substrates on the carboxyl side of aspartate residues. Activation of these caspases is the main step in cells undergoing apoptosis and occurs by sequential proteolytic events that cleave the single peptide precursor into large and small fragments.[22] The crystal structures of mature caspase-1 and caspase-3 suggest that the active caspases are composed of tetramers consisting of two molecules of each subunit.[23]

There are two major pathways involved in programmed cell death: mitochondrial (or intrinsic) pathway and the death receptor (or extrinsic) pathway.[24] These are illustrated in Figure-1. In the extrinsic pathway or Fas mediated apoptosis, the apoptotic signal is initiated by direct ligand-mediated trimerization of death receptors at the cell surface.[25] There are many known death receptors and among them the most widely studied is CD95 (cluster of differentiation 95, Fas).[26] Death receptors are a family of type I trans-membrane proteins, which belong to the tumor necrosis factor (TNF) family[27] and are expressed in several cell types. In this pathway the apoptotic process is begun by the binding of ligand (Fas-L) or anti-Fas antibodies to CD95/Fas, which then allows it to bind to the death domain of cytoplasmic proteins FADD (Fas associating death domain). This leads to the activation of procaspase-8. Active caspase-8 will activate procaspases-3, -7 and -6. Eventually this leads to the proteolysis events that are characteristic of the destruction of the cell.[27,28] In the intrinsic pathway, cytochrome *c* is released from the mitochon-

Figure-1: The pathways of the apoptotic process.

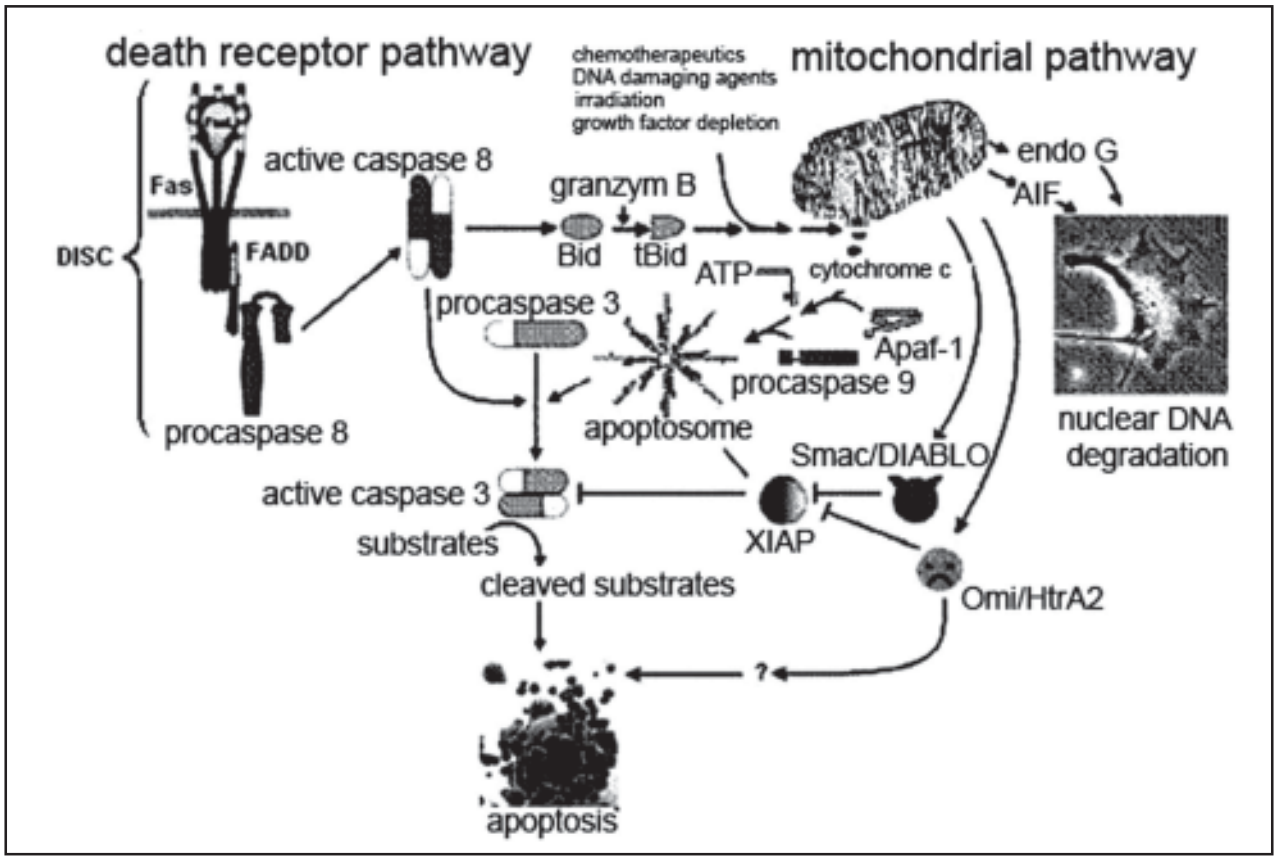

Figure-1: The pathways of the apoptotic process. In the intrinsic pathway mitochondria are triggered by many death signals such as chemotherapeutics, DNA-damaging agents, growth-factor withdrawal and irradiation. This leads to the release of multiple intermembrane space proteins including cytochrome c; AIF, apoptosis-inducing factor; endonuclease G; Smac/DIABLO (second mitochondria-derived activator of caspases/direct IAP-binding protein with low pI) and Omi/ HtrA2; high temperature requirement A. Binding of Apaf-1 to Cytochrome c induces caspase activation. Nuclear DNA degradation that is caspase - independent is induced by AIF and endonuclease G. Smac/DIABLO and Omi/HtrA2 also can induce the production of XIAP, X-linked inhibitor-of-apoptosis protein, which is the neutralized form of IAP which in turn leads to caspase activation. In extrinsic pathway, death receptors such as Fas, are ligated to their ligand (for example FasL) and results in binding the protein FADD (Fas-associated death domain) to procaspase-8 and a protein complex called DISC (death-inducing signaling complex) is formed that activates procaspase-8. Activated caspase-8 then activates caspase-3 and then activated caspase-3 begins cleavage of a variety of substrates leading to apoptosis.

dria. Also Apaf-1 (apoptotic protease activating factor-1) binds to dATP or ATP, oligomerizes and binds to cytochrome *c*. This complex activates procapase-9. Active caspase-9 binds to this complex and forms an apoptosome with a size about 700 KDa. Subsequently caspases-3, 7 and possibly 6 are activated by the apoptosome.[29] The activation of caspases-3, -6 and -7, whether by the direct action of caspase-8 or the formation of a functional apoptosome, is the final common pathway in programmed cell death. Approximately 40 proteins are cleaved by caspases in cells undergoing apoptosis.[30]

The apoptotic process is regulated by the protein superfamily Bcl-2 (B-cell lymphoma 2), of which at least 15 family members have been identified in mammalian cells and several others in viruses.[31] These proteins have a major role in preventing cell death mediated by most stimuli. In conclusion for the apoptotic process, it is clear that the health of multicellular organisms depends not only on the body's ability to produce new cells but also on controlled

cell death. Changes in cell survival contribute to the pathogenesis of disorders such as cancers, many viral infections, neuropathies and immunopathies. In other words, apoptosis permits the safe disposal of cells when they have fulfilled their intended biological function.

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