Apoptosis

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At the present moment as you read this article millions of your cells are dying. Most are sacrificing themselves to ensure your survival. Cell death is a part of a strategy for survival of the organism. This critical process, called apoptosis was overlooked for decades.

Historical Aspects: - The term programmed cell death was coined by Lockshin in 1969. The term apoptosis as originally envisaged by Kerr et al in 1972 has a broad morphological & kinetic definition while programmed cell death has a developmental and at least implied genetic basis.

Cell death can be classified as follows:

Cell Murder & (Necrosis)	Cell Suicide a. Apoptotic (Type 1)	b. Non-apoptotic · Type 2 · Type 3 · Differentiation

Types of Cell Death (Clarke 1990)

Type 1: Where there is clear cell shrinkage or condensation accompanied by chromatin condensation along margins of the nucleus.

Type 2: Previously described by Lockshin & Williams in 1964, is characterised chiefly by the appearance of an increasing number of autophagic vacuoles leading to eventual cell fragmentation.

Type 3: In this kind of atrophic cell death, the cell is deprived of essential trophic factor.

Differentiation: It is logical to regard cellular or cytodifferentiation as differentiation to death, since most differentiated cells are postmitotic and never regain the ability to reproduce and divide.

Cellular Events in Apoptosis: The morphological changes themselves involve nucleus, cytoplasm and plasma membranes. The apoptotic cells round up, lose contact with neighbours and condense or shrink.

Nuclear Events: One important characteristic of apoptosis appears to be DNA fragmentation. The enzymes that catalyse this fragmentation are usually non-lysosomal nuclear endonucleases.

Cytoplasmic Events: Loss of water experienced by cells early on in apoptosis leads to an increase in density. The cells shrink and eventually break up into smaller, spherical apoptotic particles.

Plasma Membrane Events: One important aspect of apoptosis involves phagocytosis of apoptotic fragments and the recognition of apoptotic bodies by other cells and involves a number of plasma membrane based mechanisms (Savill 1990). Mechanisms involve loss of sialic acid and exposure of glycoprotein side chain sugars. Another mechanism involves exposure and binding with phosphatidyl serine.

A third mechanism involves secretion of thrombospondin by macrophages to form a molecular bridge between the apoptotic plasma membrane and macrophage membrane.

Genetic Regulation of Apoptosis: To date, the genetic basis of programmed cell death has only been definitively

shown in a few cases and relates to developmentally induced cell death.

Oncogens, tumor suppressor genes and proteases that control apoptosis:

Bcl-2 / Bax family and apoptosis

First identified on human chromosomes18. In encodes a membrane associated protein, Bcl-2 present in ER, nuclear and outer mitochondrial membranes which has an antiapoptotic function. Bcl-2 family consists of a number of proteins and can be functionally divided into proapoptotic and antiapoptotic. These family members bind to each other to form dimers and it is probably the balances of proapoptotic and antiapoptotic Bcl-2 family proteins which determines the outcome.

P53: Tumor suppressor gene. It is a nucleo-protein which initiates cell cycle arrest or apoptosis. When cells are exposed to DNA damaging agents p53 increases in concentration and causes an increase in Bax and decrease in Bcl-2 causing apoptosis.

Proteases: Interleukin 1-B converting enzymes like family. Caspase 1 to 10 have been identified. They act by cleaving DNA, cleave cytoskeletal proteins and cause loss of cell adhesion.

Mechanism of apoptosis: Signal to initiate apoptosis may come:

a) From within the cell eg. following damage to the genome.
b) External signal — eg. May result from binding of a cell surface death receptor.

External Signal

a) Fas receptor
b) TNF receptor — Integral membrane Proteins

Activated by binding of complementary death activator (FasL & TNF respectively). Singalling of the primed cell causes activation of the caspase family which then cleave cytoskeletal proteins and DNA and cause cell death.

Internal Signal: In healthy cell outer membrane of a mitochondria, ER, & nuclear envelope express Bcl-2 on their surface, which is bound to Apaf-1 and caspase 9, which then get activated by internal damage to the cell ultimately resulting in cell death.

Apoptosis in health and disease: Cell death is important in embryogenesis and development. It has also been implied in the causation of cancer, AIDS, and autoimmune diseases. It also accounts for much cell death in Alzheimer's disease, Parkinson's disease, IHD and strokes.

Apoptosis in Obstetrics and Gynaecology: Plays an important role in:

1. Ovarian (Christin et al 1999) and corpus luteal function (Kokawa et al 1998)
2. Endometrial shedding (Jones et al 1998)
3. Endometriosis (Nakahara and Saito 1998)
4. Mammary gland (Dacly and Wohlhueter 1999)
5. Genital cancers (Waggoner et al 1998)

In Obstetrics, it is important in fetal development. Apoptosis plays a role in fetal limb development & regression of Mullerian Ducts in male (Lee et al 1998). Bcl-2 present in the fetal endometrium protects it from apoptosis. Absence of Bcl-2 in the embryonal uterine septum results in apoptosis and may be a mechanism by which the septum regresses. (Lee et al 1998).

Placental apoptosis is increased in post-term pregnancies and IUGR. (Smith and Baker 1999)

Apoptosis plays a role in immunology of pregnancy. (Warnar et al 1998)

In Vitro Fertilisation (IVF):

Apoptosis regulates the balance between development and fragmentation of embryo. It may cause excessive fragmentation in the embryo or in the granulose lutein cells and affect IVF outcome.

Conclusion

Progress in the molecular understanding of

apoptosis has been rapid. It is clear that cell death is a potentially manipulable process and there may be benefit from genetic manipulation of apoptosis. Study of cell death has indicated new therapeutic possibilities and future developments are awaited with interest.

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