PROGRAMMED CELL DEATH (PCD)

Essay

Submitted for Partial Fulfillment of Master Degree

Medical Microbiology and Immunology

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2010

Abstract

The process of programmed cell death (apoptosis) is generally characterized by distinct morphological characteristics and energy-dependent biochemical mechanisms. Apoptosis is considered a vital component of various processes including normal cell turnover, proper development and functioning of the immune system, hormone-dependent atrophy, embryonic development and chemical-induced cell death. Inappropriate apoptosis, either too little or too much is a factor in many human conditions including; neurodegenerative diseases, ischemic damage, autoimmune disorders and many types of cancer. The ability to modulate the life or death of a cell is recognized for its immense therapeutic potential. Therefore, research continues to focus on the elucidation and analysis of the cell cycle machinery and signaling pathways that control cell cycle arrest and apoptosis. To that end, the field of apoptosis research has been moving forward at an alarmingly rapid rate. Although many of the key apoptotic proteins have been identified, the molecular mechanisms of action or inaction of these proteins remain to be elucidated.

Key word:

DEATH

PCD

Microbiology

ACKNOWLEDGEMENT

First of all and above all, I always feel indebted to ALLAH whose blessings can not be counted and who gave me the power to finish this essay.

I would like to express my deepest appreciation and gratitude to ***Prof. Dr. Soliman Aref Mohamed*** *Professor of Medical Microbiology and Immunology Faculty of Medicine- Cairo University for his wise guidance and kind support during this work.*

I am also indebted to ***Dr. Zeinab Abd El-Khalek*** *Assistant Professor of Medical Microbiology and Immunology, Faculty of Medicine-Cairo University for her encouragement and close supervision.*

At this limit, I can't forget the great support from my family who offered me the most suitable atmosphere to end this work.

God Bless You All

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List Of Abbreviation

AIDS	**Acquired immunodeficiency syndrome**
AIF	**Apoptosis inducing factor**
AP-1	**Activator protein -1**
Apaf-1	**Apoptosis protease activating factor-1**
APC	**Anaphase-promoting complex**
APP	**Amyloid Precursor Protein**
Apo1	**Apoptosis antigen ligand 1**
ARF	**ADP Ribosylation factors**
ATM	**Ataxia telangiectasia mutated gene**
Aven	**Cell death regulator Aven**
BAD	**BCL2 antagonist of cell death**
BAG	**BCL2 associated athanogene**
BAK	**BCL2 antagonist killer 1**
BAX	**BCL2 associated X protein**
Bcl-10	**B-cell lymphoma protein 10**
Bcl-2	**B-cell lymphoma protein 2**
Bcl-w	**BCL2 like 2 protein Apoptosis regulator**
Bcl-x	**BCL2 like 1 BCL2 related protein**
Bcl-XL	**BCL2 related protein,**
Bcl-XS	**BCL2 related protein, short isoform**
BID	**BH3 interacting domain death agonist.**
BIK	**BCL2 interacting killer**
BIM	**BCL2 interacting protein**
Blk	**Bik-like killer protein B**

Ca	**Calcium**
CAD	**Caspase activated DNase(nuclease)**
Caspase	**Cysteinyl aspartic acid-protease**
CD	**Cluster of differentiation**
CDK	**Cyclin dependent kinase**
c-FLIP	**FLICE-inhibitory protein Casper**
Chk2	**Check point kinase 2**
DED	**Death effector domain**
DR	**Death receptor**
FADD	**Fas-associated death domain**
FasL	**Fatty acid synthetase ligand**
FasR	**Fatty acid synthetase receptor**
FLICE	**FADD-like Ice**
HSP-70	**Heat shock protein-70**
HtrA2/Omi	**High-temperature requirement Omi stress regulated endoprotease**
IAP	**Inhibitor of Apoptosis Proteins**
ICAD	**Inhibitor of CAD**
IKK	**Multicomponent inhibitor protein Kinsae Kappa**
IKB α	**Inhibitor of Kappa B Kinase**
JNK pathway	**Jun N-Terminal Kinase**
MAP	**Mitogen activated protein**
Mdm2	**Murine double minute oncogene**
Myc	**Oncogene Myc c-myc**
NF-kB	**Nuclear factor-kap**
NAIP	**Neuronal apoptosis inhibitor protein**

Noxa	**Monooxygenase/tryptophan 5-monooxygenase activationprotein**
NuMA	**Nuclear mitotic apparatus protein SP-H antigen**
PARP	**Poly (ADP-ribose) polymerase**
PkB	**Protein kinase B**
Puma	**p53 up-regulated modulator of apoptosis**
RIP	**Receptor-interacting protein**
Smac/DIABLO	**Second mitochondrial activator of caspases/direct IAP binding protein with low PI**
TNFR1	**Tumor necrosis factor receptor 1**
TNF-*α*	**Tumor necrosis factor alpha**
TRADD	**TNF receptor-associated death domain**

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Programmed Cell Death (PCD)

The term apoptosis (a-po-toe-sis) was first used in a nowclassic paper by ***(Kerr et al., 1972)*** to describe a morphologically distinct form of cell death, although certain components of the apoptosis concept had been explicitly described many years previously. Our understanding of the mechanisms involved in the process of PCD in mammalian cells transpired from the investigation of PCD that occurs during the development of the nematode *Caenorhabditis elegans* ***(Horvitz, 1999)***. In this organism, 1090 somatic cells are generated in the formation of the adult worm, of which 131 of these cells undergo apoptosis. These 131 cells die at particular points during the development process, which is essentially invariant between worms, demonstrating the remarkable accuracy and control in this system. Apoptosis has since been recognized and accepted as a distinctive and important mode of PCD, which involves the genetically determined elimination of cells. However, it is important to note that other forms of PCD have been described and other forms of PCD may yet be discovered ***(Formigli et al., 2000)***.

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 ***(Norbury and Hickson, 2001)***. Although there are a wide variety of stimuli and conditions, both physiological and pathological, that can trigger apoptosis, not all cells will necessarily die in response to the same stimulus. Irradiation or drugs used for cancer chemotherapy results in DNA damage in some cells,

which can lead to apoptotic death through a *p53*-dependent pathway. Some hormones, such as corticosteroids, may lead to apoptotic death in some cells, e.g., thymocytes, although other cells are unaffected or even stimulated. Some cells express Fas or TNF receptors that can lead to apoptosis via ligand binding and protein cross-linking. Other cells have a default death pathway that must be blocked by a survival factor such as a hormone or growth factor. There is also the issue of distinguishing apoptosis from necrosis, two processes that can occur independently, sequentially, as well as simultaneously ***(Zeiss, 2003).***

In some cases, it's the type of stimuli and/or the degree of stimuli that determines if cells die by apoptosis or necrosis. At low doses, a variety of injurious stimuli such as heat, radiation, hypoxia and cytotoxic anticancer drugs can induce apoptosis but the same stimuli can result in necrosis at higher doses. Finally, apoptosis is a coordinated and often energy-dependent process that involves the activation of a group of cysteine proteases called "caspases" and a complex cascade of events that link the initiating stimuli to the final demise of the cell.

Light and electron microscopy have identified the various morphological changes that occur during apoptosis ***(Hacker, 2000)***. During the early process of apoptosis, cell shrinkage and pyknosis are visible by light microscopy ***(Kerr et al., 1972).***With cell shrinkage, the cells are smaller in size, the cytoplasm is dense and the organelles are more tightly packed. Pyknosis is the result of chromatin condensation and this is the most characteristic feature of apoptosis. On histologic examination with hematoxylin and eosin stain, apoptosis involves single cells or small clusters of cells. The apoptotic cell appears as a round or

oval mass with dark eosinophilic cytoplasm and dense purple nuclear chromatin fragments . Electron microscopy can better define the subcellular changes. Early during the chromatin condensation phase, the electron-dense nuclear material characteristically aggregates peripherally under the nuclear membrane. Extensive plasma membrane blebbing occurs followed by karyorrhexis and separation of cell fragments into apoptotic bodies during a process called "budding." Apoptotic bodies consist of cytoplasm with tightly packed organelles with or without a nuclear fragment. The organelle integrities are still maintained and all the components are enclosed within an intact plasma membrane. These bodies are subsequently phagocytosed by macrophages and degraded within phagolysosomes .

Macrophages that engulf and digest apoptotic cells are called "tingible body macrophages" and are frequently found within the reactive germinal centers of lymphoid follicles or occasionally within the thymic cortex. The tingible bodies are the bits of nuclear debris from the apoptotic cells. There is essentially no inflammatory reaction associated with the process of apoptosis nor with the removal of apoptotic cells because: (1) apoptotic cells do not release their cellular constituents into the surrounding interstitial tissue; (2) they are quickly phagocytosed by surrounding cells thus likely preventing secondary necrosis; and, (3) the engulfing cells do not produce pro-inflammatory cytokines ***(Kurosaka et al., 2003).***

Many of the genes that control the killing and engulfment processes of PCD have been identified, and the molecular mechanisms

underlying these processes have proven to be evolutionarily conserved ***(Metzstein et al., 1998)***.

Until recently, apoptosis has traditionally been considered an irreversible process with caspase activation committing a cell to death and the engulfment genes serving the purpose of dead cell removal. However, the uptake and clearance of apoptotic cells by macrophages may involve more than just the removal of cell debris. It was found that blocking engulfment genes in *C. elegans* embryos enhances cell survival when cells are subjected to weak pro-apoptotic signals ***(Hoeppner et al., 2001).***

AIM OF THE WORK

The goal of this review is to provide a general overview of current and update knowledge on the process of apoptosis including morphology, biochemistry, mechanism, regulatory factors and the role of apoptosis in health and disease.

HISTORICAL BACKGROUND

Cell death is a completely normal process in living organisms and was first discovered by scientists over 100 years ago. A German scientist Carl Vogt was first to describe the principle of programmed cell death (apoptosis) in 1842. In 1885, anatomist Walther Flemming delivered a more precise description of the process of programmed cell death (PCD). However, it was not until 1965 that the topic was resurrected. While studying tissues using electron microscopy, John Foxton Ross Kerr at University of Queensland was able to distinguish apoptosis (Greek: apo - from, ptosis - falling) from traumatic cell death***(Kerr, 1965).*** Following the publication of a Currie, as well as Andrew Wyllie, who was Currie's graduate student, at University of Aberdeen. In 1972, the trio published a seminal article in the British Journal of Cancer. Kerr had initially used the term programmed cell necrosis, but in the article, the process of natural cell death was called apoptosis. Kerr, Wyllie and Currie credited James Cormack, a professor of Greek language at University of Aberdeen, with suggesting the term apoptosis. Kerr received the Paul Ehrlich and Ludwig Darmstaedter Prize on March 14, 2000, for his description of apoptosis. He shared the prize with Boston biologist Robert Horvitz ***(O'Rourke and Ellem,2000).***

In Greek, apoptosis translates to "dropping off" of petals or leaves from plants or trees. Cormack, reintroduced the term for medical use as it had a medical meaning for the Greeks over two thousand years before. Hippocrates used the term to mean "the falling off of the bones". Galen extended its meaning to "the dropping of the scabs". "Apoptosis was used