APOPTOSIS PADA OVARIUM SEBAGAI MEKANISME KEMATIAN SEL FISIOLOGIS

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Abstrak

Dalam rangka untuk mengontrol perkembangan embrio dan juga untuk mempertahankan proses apoptosis jaringan dewasa diperlukan. Untuk memenuhi peran ini, apoptosis terjadi berdasarkan program genetik yang diaktifkan oleh rangsangan dari sinyal eksternal dan internal. Dalam ovarium sebagai organ yang menghasilkan folikel telur, hanya folikel dominan yang dibutuhkan untuk menjadi sel telur. Folikel tetap akan mengalami atresia. Dalam hal ini proses apoptosis pada wanita reproduksi merupakan strategi untuk memilih folikel dominan. Namun, itu adalah mekanisme rumit untuk mengontrol proses apoptosis yang melibatkan berbagai protein seperti Bcl-2, p53, Bax, dan Buruk telah dinyatakan dalam penelitian baru-baru ini. Mereka protein adalah bagian dari keluarga pro dan antiapoptotic. Informasi lebih lanjut diperlukan untuk memperjelas peran apoptosis sebagai mekanisme fisiologis untuk memilih folikel dominan di ovarium pada wanita reproduksi.
Kata kunci: apoptosis, ovarium, telur, folikel, atresia.

APOPTOSIS IN OVARY AS A PHYSIOLOGICAL CELL DEATH MECHANISM

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Abstract

In order to control the embryonic development and also to maintain the adult tissues apoptosis process is needed. To fulfill this roles, apoptosis occurred based on genetic program which activated by the stimulation of external and internal signals. In ovary as an organ which produced follicle for eggs, only dominant follicle is needed to be ovum. The remain follicle will undergo atresia. In this regard the apoptosis process in reproductive woman is a strategy to select the dominant follicle. However, it is a complicated mechanisms to control the apoptosis process which involved of the various protein such as Bcl-2, p53, Bax, and Bad has been revealed in recently research. Those proteins are part of the family of pro and antiapoptotic. The further information is needed to clarify the roles of apoptosis as a physiological mechanism to select the dominant follicle in ovary in reproductive woman.

Key words: apoptosis, ovary, egg, follicle, atresia.

Introduction

Apoptosis or program cell death has a key role both ini the maintain of adult tissues and embryonic development. In this roles, apoptosis is differ from accidental death of cells resulting from injury, i.e. apoptosis is an active process in which genes are responsible for both the regulation or execution. It was first recognized by pathologist in 1972, named after Greek word for "falling off," or "dropping of leaves." In other word, apoptosis is the removal of cells by cell death.

It is hypothesized that apoptosis occurred as result of a genetic program activated by developmental and environmental stimuli. Basically, apoptosis is trigerred by internal and external signals. Furthermore, the survival of organism is dependent on its cells replication. For this reason the control of replication is essential and though there is a number of protein that act as a cell cycle brake.

The objective of this writing is to show the role of apoptosis in follicular atresia. In this regard in a female's ovaries contain an estimated 2-4 million eggs in

utero. Only 200 000 – 400 000 afollicles remain in the beginning of active reproduction. Of these, all but about 400 are destined for atresia during woman's reproductive life. So, 99.99% of the ovarian follicle present at birth will undergo atresia.

Apoptosis phenomenon

Apoptosisis is a normal feature of the differentiation anf maturation of an organism, and the number of division of all types of cells is precisely controlled. Therefoyre, we dcan think that the rate of growth is the result of cell proliferation minus cell death. This is the strategy of organism to select certain cells for survival and also is a complementary but opposite role of mitosis in regulation of animal cell populations.

Numerous protein involved in apoptosis mechanisms. Recent evidence has shown that Bcl-2 family and p53 takes a role. Bcl-2 family consist of anti-apoptosis e.g Bcl-XL and proapoptosis Bax, Bad. P53 is a transcription factor, involved in apoptosis following DNA damage. The mutation of p53 will increase the carcinogenesis.

In the development of the fetal nervous system, over one half of neurons that exist in the early fetus are lost by apoptosis during development to form the mature brain. In the production of immune competent T cells a selecxtion process occurs that eliminates cells recognize and react against self.

In ovary, by eliminating the cell death gene Bax in mice, researchers have extended the life span of the animal's ovary into old age. For every cell, there is a timeto live and a time to die. However, in what ways the cells shall die? It was apparently through:

a. Killed by injurious, and
b. Induced to commit suicide. They are also responsible for a cell commit suicide.

There are two different mechanisms by which a cell commits suicide by apoptosis:

a. Signals arising within the cell,
b. Triggered by death activators such as:
- tumor necrosis factor alpha (TNF-□)
- Lymphotoxin
- Fas ligand

The signals arising within the cell or by internal signals are:

1. □cl-2 (□-cell leukemia/lymphoma) is a protein which express on the membrane of mitochondria. Bcl-2 is bound to a molecule of the protein Apaf-1 (apoptotic protease activation factor).
2. Cytochrome C (an enzyme of cellular respiraton is released into cytosol from mitochondria) + Apaf-1 bind to molecule Caspase 9.

The signals or triggered by activators such as TNF, Fas ligand. And also the initiators of apoptosis include anticancer drugs such as IL-1, growth factors, glucocorticoid, some virals protein, and various other cytokines.

In this regard, the characteristics of a normal physiological response to specific suicide signals, or lack of survival signals:

A. Chromatin condenses and migrates to nuclear membrane
B. Internucleosomal cleavage
C. Cytoplasm shrinks without membrane rupture
D. Blebbing of plasma and nuclear membrane
E. Cell contents are package to be engulfed by neighbours
F. Epitopes appears on plasma membrane marking cell as a phagocytic target.

Signals for apoptosis, on the other hand promote the action of specific calcium and magnesium dependent endonuclease that cleavages the double stranded DNA at linker regions between nucleosomes. Sustained increases in intracellular free calcium precedes apoptosis, in other word if the amount of free calcium can be reduced, the onset of apoptosis can be delayed. How the calcium might act is via the IP3, the second messenger which

promotes the release of Ca++ from internal stores.

An insider look to apoptosis in ovary.

Recent studies indicate that apoptosis occurs in the ovary during follicular atresia in several animal species, including the rat, pig, chicken, baboon, and rabbit. In line to the objectives of this writing, let us look into the oogenesis in brief:

The germ cedlls or oogonia which undergo mitotic division during development in utero. Three months after conception, the oogonia develop into primaty oocytes, which begin a first meiotic division by replicating their DNA. The division is not complete until puberty (meiotic arrest). Only primary oocyt which destined for ovulation will ever complete the first meiotic division to be secondary oocyte is fertilized. The other parts of division which lack of cytoplasma is called polar body.

The net result of oogenesis is that each primary oocyte can produce only one ovum. The ovum exist in structures known as follicle. Follicle begins as primary follicles, which surrounded by granulose cells, theca cells and zona pellucid. Only one dominant follicle continous to develop, and other follicle has begun to undergo degenerative called atresia.

Thus, it appears that follicle atresia is one example of apoptosis or program cell death in oogenesis and follicle growth.

In case of ovary, the apoptosis occurred in:
a.Female germ cells, oogonia and oocyte during fetal development
b.granulosa cells, follicular atresia during reproduction period

The only one follicle which has been selected for ovulation, while others undergoes atresia. The initiation of apoptosis is in granulose cells,, which has been documented by both morphological and biochemical criteria. In this relation, the FSH and LH are endocrine factors responsible for inhibiting apoptosis in granulose cells of developing follicles. And for the sake or paracrine factors which are responsible for apoptosis is progesterone for activating apoptosis, while estrogen, growth hormone (GH) via insulin like growth factor-I (ILGF-I) for inhibiting apoptosis. The other hormone which prevent the apoptosis is gonadotropin and induction by androgen and GnRH.

Pathways of apoptosis in normal ovary is regulated in all p53 and Bcl-2 family of genes. These genes play a role, activating either as inhibitor or promotes of apoptosis. Along with apoptosis mechanism, the follicular atresia is known to occur by apoptosis, but the molecular triggers for these process are not understand. Currently, it has been hypothesized that the Fas antigen is a potential role as a transmembrane receptors which triggers apoptosis. The Fas antigen share homology with a family receptors including TNF receptor, NGF receptor.

Atretic follicles have increased DNA fragmentation and expression of Fas gene resulting in apoptosis in rats and humans, and these may be used to detect apoptosis in atretic Bovine follicles. Also atretic follicles express less cytochrome P450 17□-hydroxylase (P450 c17), P450 scc, P450 arom, mRNA than healthy follicles. And LH increased may decrease apoptosis and expression of Fas gene.

At last, the ovary has proven to be an excellent model to study the role of cell death genes in a physiological setting of endocrine-reguulated apoptosis.

So, the meaning of apoptosis:
The inhibition of apoptosis may contribute to disease, and a high rate of apoptosis probably contributes to degenerative disease such as osteoporosis. In other meaning, that is mutation in the p53 gene, producing a defective protein, for example in cancer cells.

Apoptosis is an attribute as needed for proper development as mitosis and also is needed to destroy cells that represent a threat to integrity of organism.

Conclusions:

1. Apoptosis is the strategy of organism to select certain cells to survival
2. It is hypothesized occurred as result of a genetic program activated by developmental and environmental stimuli.
3. Control of apoptosis through signals pathway and the genes.
4. Death signals are integrated by specific intracellular, modulated and targeted activate a cascade of cycteine protease called Caspase.
5. The stages of apoptosis may be considered as initiation, genetic regulation, and effector mechanism.
6. Less than 1% of the follicles present in the ovary are destined to ovulate, while the majority become atretic.
7. The non-selected follicle is terminated by the process of atresia.
8. Granulosa cells are lost by apoptosis at the onset of follicular atresia.

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