

Possible Role of Placental Apoptosis in Etiopathogenesis of Preeclampsia

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Abstract

The course of pregnancy in 6-8% cases is complicated by preeclampsia, and every year it is responsible for about 50000 maternal deaths all over the world. Etiology of preeclampsia is unknown. Currently the following hypotheses related to the etiology of preeclampsia are popular: a) placental ischemia; b) endothelial dysfunction; c) immunologic maladaptation; d) genetic and e) elevated peroxide oxidation of lipids. Abnormal invasion of trophoblast when spiral arteries are replaced by trophoblast is considered as one of the major pathogenetic factors in the pathogenesis of preeclampsia. Placental apoptosis was indicated as the cause of abnormal invasion of trophoblast in several papers. Recently intensive studies to investigate the phenomenon of "cellular suicide" have been carried out. Apoptosis is involved in the development of widely spread diseases. There are data indicating that the onset of preeclampsia is always accompanied by apoptosis. We believe that apoptosis may become a key possibly to several locks hiding the secrets of preeclampsia pathogenesis.

Keywords: *preeclampsia, placental apoptosis, trophoblast invasion*

Intercellular relationship in multicellular organisms is attracting the researchers for a long time. And this is not accidental since these relationships are triggering cells to enter various phases of their life such as division, growth, development, differentiation and, as it was found out just recently, death. It should be noted that researchers paid considerably less attention to the problem of cellular death than other stages of the cell life even though the first considerations about the existence of the process of cellular death in multicellular organism appeared as early as in the end of XIX c. [1]

Apoptosis (from Greek apo- separation +ptosis - fall), means fall of the leaves - is a recognized term for programmed death of the cells. The term "apoptosis" was first used by Hippocrates. This word is also encountered in the works of Galen. Much later, since

1972 this term was used to indicate programmed cellular death when Kerr, Wyllie and Currie published the article in British Journal of Cancer. [2] To the importance of the apoptosis problem as one of the mechanisms regulating existence of nearly all living organisms on the Earth testifies the fact that in 2002 Sidney Brenner and John Sulston from Great Britain and American Robert Horvitz received Nobel Prize in medicine "for discoveries in the sphere of genetic regulation of organs development and programmed death of the cells". The above researchers made their revolutionary discoveries thanks to the experiments on small, transparent vermines - nematodes (nematode *Caenorhabditis elegans*). Sidney Brenner realized that investigation of unicellular organisms would not take him far, while mammals are too complicated to tackle with. Sydney Brenner found out that "misprints" in genetic

code of animals - mutations are capable to lead to the impairment of animal organs and tissues.

John Sulston also used nematodes to study cellular differentiation - the process during which initially identical embryonic cells are transforming into the muscular, blood or neuron cells. Besides, Sulston experimentally confirmed the truth of philosophic postulate saying that life and death are one integer whole. "Death genes" are mandatory for the growth and development of the organism. They induce excessive cells to commit suicide and then remove them from the organism.

Robert Horvitz in 1986 isolated "death genes" called *ced-3* and *ced-4*, as well as thoroughly investigated the mechanism of apoptosis. At the same time, he isolated one more gene *ced-9*, which is blocking activity of *ced-4* gene thus protecting cell from the death. Subsequently it was found out that many genes of nematode discovered by Brenner, Sulston and Horvitz have their analogues in humans.

Apoptosis is a physiological process. Evidently the phenomenon of apoptosis developed in the process of evolution and coincided with the appearance of multicellular organisms to regulate the number of cells and establish certain relationships between individual cells in integer organism. [1] At the first stage a cell receives "message" saying that it shall sacrifice its life for the benefit of the organism. This message arrives from external sources - either from neighboring cells or from intercellular substances solid or liquid. Such "message" is perceived by the receptors. External part of the receptor is capable to recognize the molecules of strictly specific structure which can either freely float in extracellular fluid or be fixed on the surface of other cells or intercellular fibers. Signal molecules and receptors fit to each other like a key and a lock. Information is transferred through various receptors or receptors combination. Absence of specific substance in the medium surrounding a cell can also serve as information. It is well known that in some cases even silent telephone can eloquently speak. [3]

Apoptosis is a fundamental biological, energetically active, genetically controlled process required to remove damaged, old and infected cells. Apoptosis plays a leading role in tissues embryogenesis and involution, supporting homeostasis, maintaining cellular balance under physiological conditions. It is responsible for removal of excessive cells particularly in nervous and immune system. [4] Presently it became evident that programmed cellular death is an important mechanism of maintaining correct number of cells in multicellular organism. [5] Conditionally the process of apoptosis consists of three stages. First stage includes interaction between extra- and intracellular signals to decide whether cell shall "live" or "die". The second stage includes DNA fragmentation, which is visually

manifested by condensation of nuclear chromatin and division of a nucleus. Subsequent proteolysis leads to cellular disintegration into the so-called "apoptosis bodies" containing externally intact mitochondria and other organelles. The third stage ends with complete disappearance of the cell as a result of phagocytosis of the "apoptosis bodies" caused by "professional" and "non-professional" macrophages without any contact of their contents with surrounding medium which distinguishes apoptosis from necroses or other types of cellular disintegration. [6] Necrosis is related to complete metabolic collapse leading to cellular edema, early loss of its integrity, impairment of mitochondria and other organelles, which eventually ends with the lysis of cellular remnants. Cellular necrosis becomes the cause of damage and inflammation of surrounding cells, while in the process of apoptosis a cell completely disappears within 15-120 minutes. [7]

There are three leading factors triggering apoptosis:

1. Increasing of expansion of apoptosis inducing genes;
2. Suppression of apoptosis inhibiting genes;
3. Enhanced calcium intake by the cell. [8]

The majority of factors causing cellular necrosis in small doses can also initiate apoptosis. Those are oxidants, anti-tumor preparations, toxins. The same role may play such non-specific factors as temperature, free radicals, g- and UV-radiation, etc. In all those cases apoptosis is induced, however if the dose of the respective agent is increased it results in development of cellular necrosis. More than ten viral genes are known to code factors increasing the process of apoptosis (adenoviruses, herpes viruses, papilloma viruses, influenza virus, HIV, hepatitis B virus etc.).

Apoptosis phenomenon is the result of the action of various factors leading to death of a cell. Since apoptosis is a physiological phenomenon the organism must have factors leading to cellular apoptosis. By now it is known that apoptosis can be induced both by intracellular signals and external factors acting through receptor systems, which are non-toxic or destructive per se. 1.

It is long known in endocrinology that removal of endocrine gland leads to mass involution of target cells. The mechanism of this phenomenon remained unknown until discovery of apoptosis phenomenon which stimulated investigation of the processes underlying the effect of hormones on the viability of cells. Thus, castration leads to the atrophy of prostate glandular cells. Administration of androgens prevents this process. In other words, androgens are inhibitors of apoptosis for the prostate cells. At the same time they are apoptosis inducers for follicular cells of the ovaries. This example illustrates how one and the same hormones can be apoptosis inhibitors for one type of cells and inducers - for the other. The various effects of

apoptosis regulation by one and the same hormone depending on the stage of cellular differentiation have also been studied. Thus estrogens are inhibitors of uterine endothelial cells apoptosis in the beginning of menstrual cycle, while the same estrogens became apoptosis inducers at the end of the cycle. Progesterone will be the inhibitor of uterine epithelium apoptosis at the end of the cycle. The effect of the hormone is exerted through specific receptors. Receptor through binding a ligand regulates transcription of hormone-susceptible genes. Those can be either genes the products of which are regulating passage of a cell through cellular cycle or apoptosis-specific genes. [1] Hormones action is distinguished by its specificity that is manifested not only on organ level but also within various sites of one and the same tissue.

The other important physiological regulators of apoptosis are cytokines. Cytokines are a vast group of proteins regulating proliferation and differentiation of the cells in the process of binding to specific receptors on the target cells. Unlike hormones cytokines effect is manifested mainly at para- and autocrine levels. Cytokines are subdivided into 3 large groups: growth factors (colony stimulating factors, epidermal growth factor, insulin-like growth factor etc.); the family of tumor necrosis factor (TNF) and spiral cytokines, interleukins, interferon). The effect of cytokines on cells is also different: for one cells cytokines play the role of apoptosis inducer, while for others - of apoptosis inhibitor. It depends on the type of the cell, stage of its differentiation, and its functional state. The sequence of events leading the cell to apoptosis as a result of interaction of TNF family proteins with specific receptors has been studied best of all. One of the representatives of this group of proteins is the system Fas/Fas-L. The first specialized receptor for apoptosis induction CD95(Fas/APO-1) was discovered on cytoplasmic membrane of the cells about ten years ago. Binding of monoclonal antibodies (MCA) or specific ligand CD95L/FasL with the receptor induces apoptosis in susceptible cells. It should be mentioned that this system is known to have no other functions except for induction of cellular apoptosis. Fas/APO-1/CD-95 is a receptor, which by its structure belongs to the TNF? family receptors. Interaction of Fas with Fas-L (ligand) or monoclonal antibodies leads to cellular apoptosis. Fas constitutively is expressed on the surface of many types of the cells such as: thymocytes, lymphoblastoid cellular lines, activated T- and B-lymphocytes as well as fibroblasts, hepatocytes, keratinocytes, myeloid cells. Fas gene in humans is localized in the long arm of the chromosome 10 and consists of 9 exons.

Fas-L is a cytokine and belongs to the family of TNF? Fas-L is expressed on the activated T-lymphocytes and natural killer cells as well as on Sertoli's cells and parenchymal cells of the anterior chamber of the eye, which allows these cells to kill any Fas-expressing cell including activated T-lymphocytes. This mechanism

determines appearance of areas protected from immune system. This phenomenon is known under the term immune privilege.

Other cytokines - interleukins and interferon play important role in regulation of apoptosis of immune system cells. Intensive research is being conducted to find out apoptogenic action of interleukins (IL). They were found out to be the apoptosis inducers both in healthy and oncologic cells and cellular lines. However apart from apoptosis inducer features interleukins have equally expressed apoptotic preventive effect of cytokines. One and the same IL can be both apoptosis inducer and inhibitor. Differences in cellular response of various target cells are possibly depending on the degree of their differentiation and development.

Interferons (IF) role in effecting the cells is also dual. In some cases IF induces bone marrow cells apoptosis, while in others it inhibits the apoptogenic signal peripheral human monocytes). Interesting data are related to the apoptosis regulation through peptide growth factors. There are convincing data testifying that growth factors prevent apoptosis development in the cells. Elimination of growth factors from the cell culture leads to typical apoptotic manifestations.

Proteases seem to play a central role in triggering and development of apoptosis process. This group of proteases called caspases exists aloof and functions as a mediator of death signal. So far ten caspases generating enzyme cascade similar to that of blood clotting system or complement system have been found out in various mammalian cells. Caspases are subdivided into effectors, i.e. enzymes directly hydrolyzing structural proteins of the cell and inductors - caspases receiving apoptotic signal and transferring it to effector caspases. Many proteins degradation of which causes irreversible processes characteristic of apoptosis are known to be molecular targets for caspases-effectors. Caspases are present in the cell constitutively (event in the neurons, that are not revived during their life-span), which allows to rapidly induce apoptosis. One of the ways of caspases activation is related to interaction of apoptosis inducer with specific receptors (e.g. caspase-8 activation in the course of Fas ligand interaction with Fas-receptor). Another way is caspase-9 activation as a result of heterodimers formation by the family of Bcl-2 proteins. [1]

Apoptosis is a standard response to DNA impairment. Cellular apoptosis begins from the moment of DNA impairment which interrupts its reproduction cycle. If DNA is not "repaired" the cells enter the phase of apoptotic death. [9,10]

Increase of the survival ability of the cell, that is apoptosis inhibition, results in development of cancer, autoimmune diseases and viral infections,

neuroproliferative diseases such as schizophrenia and autism, etc. Decrease of survival ability of the cells and consequently apoptosis activation plays a role in the pathogenesis of AIDS, neurodegenerative diseases such as Alzheimer's disease, Parkinson disease, ischemic states such as stroke and infarction, diabetes, hydronephrosis and others. As it is evident from the above said, apoptosis is involved in the development of most widespread diseases. Proceeding from the above one can suppose that participation of "cellular suicide" is a mandatory part of obstetrical pathology of pregnant women expressed by pre-eclampsia - one of the most mysterious diseases, pathogenesis of which contain many blank pages. Studies to define the role of apoptosis in pre-eclampsia development have a short history but this direction is gradually becoming a priority. Scientists have noticed that placenta is necessary for development of pre-eclampsia. The following facts testify in favor of such argument:

- in hydatidiform mole when there is trophoblast but no fetal tissue pre-eclampsia is revealed earlier, its incidence is significantly higher than on the background of the routine pregnancy;

- If after the birth the parts of placenta are delayed, disease signs will be maintained in postpartum period as well until placenta is completely removed from the maternal organism.

Of all hypotheses explaining pre-eclampsia etiology the following are currently very popular:

1. Hypothesis of placental ischemia, when after pathological invasion of trophoblast into the spiral maternal arteries, placental perfusion decreases resulting in placental hypoxia followed by generation of toxic mediators (cytokines, reactive oxygen species) by the uterine-and-placental complex causing diffuse endothelial dysfunction, that in its turn is followed by manifestation of clinical symptoms of pre-eclampsia.

2. Hypothesis of immunologic maladaptation, when pathological immunologic response of maternal organism accompanied with overgrowth of decidual tissue cytokines production, proteolytic enzymes and free radicals causing endothelial dysfunction after abnormal follows trophoblast invasion.

3. Hypothesis of endothelial dysfunction, when in the course of pregnancy system inflammatory response involving clotting factors and complement system is impaired.

4. Genetic hypothesis, when a change in genetic imprinting may cause a single recessive gene or a dominant gene with incomplete penetrance to become activated during pregnancy.

5. Hypothesis of elevated peroxide oxidation of lipids when attenuation of placental antioxidant protection results in uncontrolled peroxide oxidation of lipids with the rise of thromboxane and TNF, after which follows leukocytes activation in intervillous space thus causing increase of oxidative stress and endothelial dysfunction. [15,16]

Evidently, abnormal, superficial trophoblast invasion is the key moment in the first two hypotheses. In normally implanted placenta endothelium and internal elastic layer of uterine spiral arteries is replaced by trophoblasts and these arteries increase their diameter 4-6 times compared with that of non-pregnant women. In superficial invasion spiral arteries are only partially filled by trophoblasts and arteries and enlargement of the arteries diameter reaches only 40% of that observed in normal pregnancy thus resulting in insufficient blood supply to the placenta.

Let us consider a number of works where abnormal trophoblast invasion is considered as a triggering point in the pathogenesis of preeclampsia.

Inadequate trophoblast invasion is believed to initiate placental ischemia. [17]

According to some data, diminution of placental perfusion is a result of abnormal trophoblast invasion. [18]

Defective placental invasion leads to placental hypoxia and insufficient perfusion with subsequent damage and dysfunction of endothelial cells and hence preeclampsia. [19,20]

According to the existing hypothesis pathological invasion followed by interrupted perfusion leads to preeclampsia. [21]

The studies conducted demonstrated that insufficient trophoblast invasion into the maternal spiral arteries can be a possible cause of preeclampsia onset. [22] Pathomorphologic studies of placenta demonstrated superficial trophoblast invasion during preeclampsia. [23]

Redman CW considers placental ischemia as a cause of preeclampsia. He presents preeclampsia as a two-stage disease: Stage I is limitation of spiral arteries area (poor placentation) or their obstruction (acute atherosclerosis). Stage II - placental ischemia with consequent development of diffuse endothelial dysfunction. [24]

Impaired trophoblast invasion into the spiral arteries is a key to the mechanism of preeclampsia. According to the authors macrophages located on placental bed hinder trophoblast invasion. Mechanism of macrophage activation is unknown. [25,26]

Works have been published where placental apoptosis was indicated as the cause of abnormal trophoblast invasion. [27]

Apoptosis plays an important role in endometrial decidualization and trophoblast invasion. [7]

Apoptosis is caused by binding of FAS with FAS ligand (FASL). Evidence based data on apoptosis in placental tissues are probably related to the presence of FASL in trophoblasts. FASL-initiated apoptosis possibly plays a role in the process of trophoblast invasion and implantation. [28,29]

Placental apoptosis and increased expression of FAS and FASL in trophoblasts probably play a role in pathogenesis of preeclampsia. [30]

There is a hypothesis claiming that apoptosis is a key to the pathophysiology of placental hypoxia and that Bcl-2 gene influences this process through apoptosis inhibition. [31]

According to some data, thromboxane A2 contributes to placental dysfunction via restriction of differentiation and enhancement apoptosis in trophoblasts. [32]

Placental hypoxia is related to enhanced apoptosis in trophoblasts. Apoptosis is associated with increased expression of genes p53 and Bax and decreased expression of Bcl-2. [33]

Antibodies Anti-Anexin V are binding with the trophoblast cells and induce placental apoptosis. It may

be the very pathogenic mechanism through which antibodies induce defective placentation. [34]

In preeclampsia etiology participated TNF (Physiological activator of apoptosis). [35]

At the same time according to some data preeclampsia is associated with cytotrophoblasts apoptosis. [36,37]

Preeclampsia is associated with superficial invasion of cytotrophoblast and enhanced apoptosis in trophoblasts. Heparin-binding epidermal-growth-factor-like growth factor (HB-EGF) has an expressed cytoprotective activity and is an important signal protein regulating trophoblast invasion during early stages of implantation. Decrease of HB-EGF is indicative of a week differentiation and superficial trophoblast invasion, leading to diminution of placental perfusion and hypertension. [38]

Thus, it seems that apoptotic process plays a significant role in pathological trophoblast invasion which in fact is a starting point in the hypotheses of placental ischemia and immunologic maladaptation. Considering the fact that programmed cellular death is a genetically controlled process, as well as the fact that initiation of cellular suicide occurs on the background of increased peroxide oxidation of lipids and oxidative stress 19 as well as considering important role of Fas/FasL system in systemic inflammatory response, it is assumed that apoptosis can become a sort of connection bridge between the most distributed theories. The first results of the studies started by us also confirm the assumption about paramount importance of finding out apoptosis role in pathogenesis of preeclampsia.

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Возможная роль плацентарного апоптоза в этиопатогенезе преэклампсии

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Р Е З Ю М Е

Течение 6-8% всех беременностей осложняется преэклампсией и уносит ежегодно во всем мире приблизительно 50000 материнских жизней. Этиология преэклампсии неизвестна. На сегодняшний день популярны гипотезы: а) плацентарной ишемии, б) эндотелиальной дисфункции, с) иммунологической дисадаптации, d) генетическая и е) гипотеза повышенной пероксидной оксидации липидов. В патогенезе преэклампсии аномальная инвазия трофобласта считается одним из главных патогенетическим факторов, когда замещение спиральных артерий трофобластом происходит частично. Появились работы, в которых причиной аномальной инвазии трофобласта считается плацентарный апоптоз. В последние годы ведутся интенсивные работы по изучению феномена возникновения "клеточного суицида". Апоптоз вовлечен в развитие самых распространенных болезней. Имеются сведения, что и возникновение преэклампсии не обходится без участия апоптоза. По нашему мнению, апоптоз может стать ключом к раскрытию нескольких звеньев патогенеза преэклампсии.

Ключевые слова: *преэклампсия, плацентарный апоптоз, инвазия трофобласта*