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Role of genes involved in the regulation of apoptosis in the pathogenesis of genital endometriosis. A literature review

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BACKGROUND: The high prevalence, the lack of reliable data on the etiology, as well as the complexity of diagnosis and treatment of genital endometriosis indicate the urgency of the problem.

AIM: The aim of this study was to analyze and summarize scientific publications devoted to the study of single-nucleotide polymorphisms involved in apoptosis and their association with endometriosis.

MATERIALS AND METHODS: Based on keyword searches for "gene," "SNP," "apoptosis," and "endometriosis," a selection of papers published in open sources (PubMed and Google Scholar) in the period from 2010 to 2020 was performed.

RESULTS AND CONCLUSIONS: An analysis of the main and auxiliary apoptotic pathways was performed, with the protein regulators and their genes detailed in accordance with the implementation of the programmed cell death cascade in genital endometriosis. The review identified the significance of a number of proteins (TNF-α, FADD, CASP3, CASP7, CASP10) in the pathogenesis of hyperproliferative diseases. However, many apoptotic regulators (BCL2, BIK, BMF, HRK, BAD, Survivin) in genital endometriosis were found to have been understudied, which makes future research in this direction promising.

Keywords: endometriosis; apoptosis; apoptosis regulator; gene; single-nucleotide polymorphism.

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Значение генов, участвующих в регуляции апоптоза, в патогенезе наружного генитального эндометриоза (обзор литературы)

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Обоснование. Высокая распространенность, отсутствие достоверных сведений об этиологии, а также сложность диагностики и лечения генитального эндометриоза свидетельствуют об актуальности данной проблемы.

Цель — проанализировать и обобщить научные публикации, посвященные изучению полиморфных вариантов генов, участвующих в процессах апоптоза, и их ассоциации с эндометриозом.

Материалы и методы. На основании поиска ключевых слов gene, SNP, apoptosis и endometriosis в открытых источниках (PubMed и Google Scholar) отобраны работы, опубликованные в период с 2010 по 2020 г.

Результаты и заключение. Проанализированы основные и вспомогательные пути апоптоза, детализированы особенности факторов и их генов в соответствии с реализацией каскада запрограммированной клеточной гибели при наружном генитальном эндометриозе. В ходе обзора определены значения ряда белков (TNF-α, FADD, CASP3, CASP7, CASP10) в патогенезе гиперпролиферативных заболеваний. Вместе с тем обнаружено, что многие аспекты реализации апоптоза (BCL2, BIK, BMF, HRK, BAD, Survivin) при генитальном эндометриозе изучены недостаточно, что обусловливает перспективность дальнейших исследований в данном направлении.

Ключевые слова: эндометриоз; апоптоз; факторы апоптоза; гены; полиморфизм.

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External genital endometriosis (EGE) is a disease that affects the quality of life of women, both the reproductive function and the presence of chronic pain syndrome of varying severity [1]. The absence of pregnancy with regular sexual activity is recorded in >30% of patients with EGE [2]. In patients with endometriosis, hormonal status changes, luteal phase deficiency occurs, folliculogenesis is impaired, and oocyte dysfunction is noted, affecting the quality of embryos and explaining the high risk of miscarriage [3]. In addition, pain syndrome manifests itself, not only with dysmenorrhea, but also with dyspareunia, pain during defecation, and chronic pelvic pain, which reduces performance, leading to temporary disability and psychological problems in the form of anxiety disorder [4, 5]. Thus, genital endometriosis also represents a social problem that necessitates the development of effective interventions.

Modern EGE therapy is aimed only at symptomatic treatment and only remotely affects the disease pathogenesis, including the risk of relapse [6]. Despite a long history of study and the annual appearance of several original studies, the current understanding of the etiology, and pathogenesis of the disease is unclear [7, 8]. Metaplastic, hormonal, immune, neoplastic, and genetic theories are presented for the disease onset. J.A. Sampson's theory of retrograde menstruation is the most widely accepted theory of EGE pathogenesis [7]. However, in a paradox, retrograde menstruation is widespread in women of reproductive age; however, the EGE incidence is relatively rare compared to the retrograde menstruation incidence [8]. One hypothesis presents that endometriosis registered defects in the immune system, causing the inability or insufficient efficiency in "recognition" and elimination of endometrial cells in the pelvic cavity. Inflammatory reactions play a key role at various stages in the development of hyperplastic processes, including initiation, progression, malignant transformation, invasion, and metastasis.

One of the mechanisms contributing to the survival of ectopic endometrioid cells in a "new" environment is apoptosis system impairment. Thus, in the study of apoptosis in eutopic endometrium and heterotopia in patients with endometriosis, H.M. Gebel et al. [9] reported that apoptosis in endometrial cells was significantly reduced in women with endometriosis, that is, the number of viable and active cells that enter the abdominal cavity is higher in patients who develop endometriosis. W.P. Dmowski et al. [10] showed a significantly lower index of apoptosis in the glandular epithelium in patients with endometriosis compared to that of the control group. This difference was primarily caused by a significantly decreased apoptosis during the menstrual, early proliferative, and late secretory phases of the menstrual cycle in women with endometriosis. The cyclical variability of apoptosis in these women was lost. Decreased apoptosis can be assumed to promote ectopic survival and implantation of endometrial cells, with a possible inverse correlation between the level of apoptosis and disease severity. To test this hypothesis, W.P. Dmowski et al. [10] analyzed the values of the apoptosis index based on the endometriosis grade and revealed a tendency toward a decreased apoptosis with an increased disease prevalence, but without statistically significant differences.

Currently, studies are conducted, aimed to identify the causes, as well as factors of pathogenesis for the development of new highly specific markers for non-invasive diagnostics and targeted therapy of this disease to increase the treatment efficiency. This work aimed to review the association of polymorphic variants of genes for proapoptotic and antiapoptotic factors and EGE to determine current trends, contraversions, and the most promising prospects.

At the time of writing this review in August and September 2020, a keyword search in PubMed Gene apoptosis and endometriosis identified about 520 genes, adding *homo sapiens* results in 477 candidates. Considering the large number of factors contributing to the initiation of apoptosis, the most significant proteins and their genes that are directly involved in this cascade of reactions were considered and presented in the literature over the past 10 years.

The programmed cell death is known to be implemented in five ways, three of which (main) are caspase-mediated and two are granzyme-mediated [11].

Extrinsic apoptosis pathway

The extrinsic pathway of apoptosis is the most well-known mechanism of apoptosis (sometimes described in the literature as receptor-mediated or the first pathway), which is initiated (Figure) as a result of binding of the death ligand (FASL, tumor necrosis factor-alpha [TNF-α], or TRAIL) to cell membrane receptors (TRAIL1, TRAIL2, TNFR1, and Fas). Then, it interacts through trimerization with the fas-associated death domain (FADD, a protein that interacts with the death domain of the Fas receptor), leading to the recruitment of procaspases-8 and -10 and the release of caspases-initiators-8 and -10, which activate effector caspases-3 and -7 (CASP3 and CASP7), which provokes a further caspase cascade and ends with proteolysis of the substrate and cell death. In some situations, the extrinsic pathway of apoptosis processes can interfere with the intrinsic pathway through caspase-8-mediated proteolysis of a BID-protein containing only BH3 (BH3-interacting agonist of domain death). Truncated (shortened) BID (tBID) may promote mitochondrial cytochrome release and apoptosome assembly (containing approximately 7 molecules of apoptotic protease activating factor-1 [APAF1], and the same amount of caspase-9 [CASP3] homodimers), which is typical for the intrinsic pathway activation of apoptosis processes [11, 12].

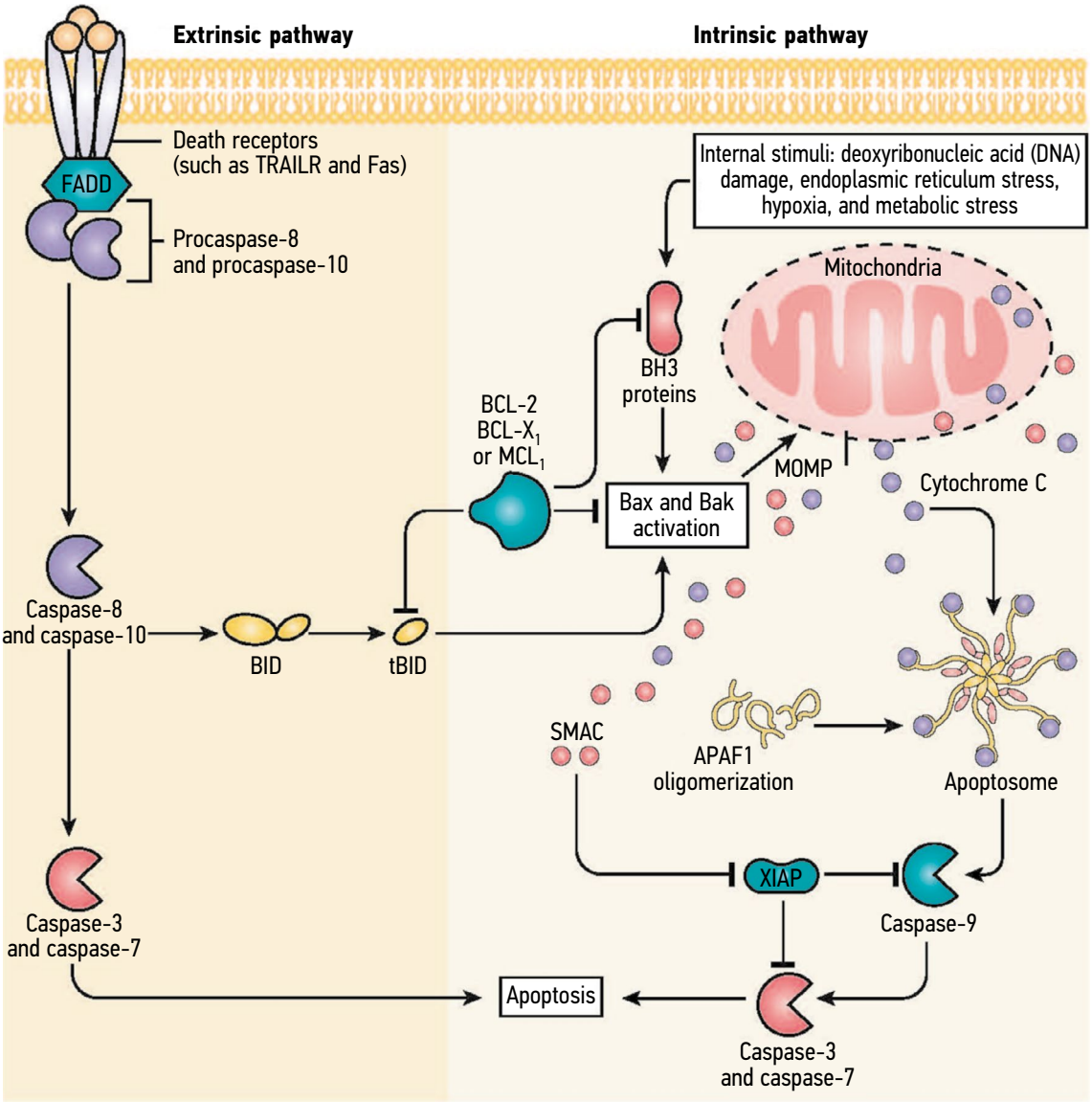

Figure. Diagram of the extrinsic and intrinsic pathways of apoptosis. Adapted from G. Ichim et al. A fate worse than death: apoptosis as an oncogenic process, 2016 [80]

Each of the factors is considered according to their role in the pathogenesis of EGE.

The "death ligands," which initiate the signaling phase of the extrinsic pathway of apoptosis, are proteins of the TNF family, which are involved not only in the process of apoptosis but also in the processes of proliferation and angiogenesis, which are also necessary for the development of EGE [13]. The most famous of these is the TNF-α (or cachexin).

TNF-α is a pro-inflammatory cytokine that plays an important role in the normal functioning of the reproductive system and the pathogenesis of some gynecological diseases, such as polycystic ovary syndrome and endometriosis [13]. Its participation in the ovulation processes and regulation of decidualization in early pregnancy, as well as in apoptosis and regeneration of endometrial tissue during the menstrual cycle was established [14]. Among the patients with endometriosis, not only a high level of TNF-α content (both in the peritoneal fluid and blood serum) was found, but also a positive correlation with disease stages [15].

A large number of single nucleotide polymorphisms (SNPs) in the *TNF*-α gene promoter may contribute to the regulation of transcription. SNPs are defined as genomic variations or differences between individuals. The SNPs in the proximal promoter of the *TNF*-α gene were described, namely a nucleotide substitution of G to A at position -238, G to A at position -308, C to T at position -857, C to A at position -863, and T to C at position -1031. Autoimmune diseases, such as rheumatoid arthritis, nonspecific ulcerative colitis, and Crohn's disease are associated with the -G308A and -C850T polymorphisms [16]. A high prevalence of -C850T polymorphism was noted in pregnant women with preeclampsia and eclampsia. The frequency of the C-allele is high in the study of the -1031T/C polymorphism in patients with uterine fibroids. Contrarily,

among patients with hyperandrogenism and polycystic ovary syndrome, a significantly low incidence of -1031T/C polymorphism was recorded [17–19].

Most researchers found no significant value for the -238G>A (in three studies), -308G>A (in five studies), -857C>T (in three studies), and -863C>A (in four studies) polymorphisms of the *TNF*-α gene in patients with EGE [20].

Study results on the SNP promoter of the *TNF*-α gene -1031T/C among patients with EGE are extremely variable and contradictory. The authors of the Australian population analysis did not reveal any significant relationship between the polymorphism of this gene and EGE [21]. Some researchers confirm the protective role of the C-allele and report a higher prevalence of the T-allele among patients with EGE, whereas others draw opposite conclusions [16, 22–24]. Data on a high prevalence rate in patients with EGE of the *TNF*-α -U01 (-1031T, -863C, and -857C) haplotype was presented, which is possible as a result of linkage disequilibrium of genes with HLAB*0702 with a close location of loci [24]. Such contradictory results may be due to differences in polymorphisms between populations or linkage disequilibrium between different polymorphisms at close gene loci [22]. Each study emphasizes the need for further searches for significant polymorphisms, as well as an increased number of samples.

TNF-α performs its function via two types of receptors, namely TNFRp55 (type 1) and TNFRp75 (type 2) [25]. A study was published on the increased prevalence (area and number of foci) of EGE in the formation of a surgical model of endometriosis in mice, knocked out by the *tnfrp55* gene [25]. However, over the past 10 years, data on the studied SNPs in the *TNFRP55* and *TNFRP75* loci are unavailable.

The next important mediator of cell and tissue apoptosis is the Fas/FASL system (apoptotic antigen 1 and its ligand), which transforms normal tissue of reproductive organs (ovaries, mammary gland, and endometrium) during the menstrual cycle in response to changes in hormone levels [26]. Fas, which is a cell surface receptor and its ligand FASL, initiate a cascade of programmed cell death when interacting with each other. These factors are known to participate in the processes of cell migration, invasion, inflammation, and proliferation [27].

One of the most frequently studied *Fas* polymorphisms is -670A/G, which decreases the promoter activity and, accordingly, the expression of this gene [28]. The association of SNP -844C/T *FASL,* with increased basal expression and transcription of the factor compared to the homozygote for the T-allele, is also known [28]. Researchers demonstrated an increased risk of preeclampsia in the presence of polymorphic variants *Fas* -670A/G, *FASL* -844C/T, and *FASL* -124A/G in a homozygous state compared with the control group [29].

A significantly increased serum Fas level was detected in patients with grades III–IV EGE compared to patients with grades I–II [30]. C.W. Pissetti et al. reported an increased incidence of *Fas* polymorphism (Rs3740286 and Rs4064) in patients with EGE in Brazil [31]. Other polymorphic variant analyses of the Fas/FASL system *Fas* (-1377G>A and -670A>G) and *FASL* (-843C>T, FASL -844C/T, and -124G/A) obtained no significant differences between patients with EGE and the control group [26, 29]. Despite the lack of significant results, S.Z. Akhavan et al. noted an increased frequency of occurrence of the ACG haplotype (Fas -670A/G, Fas -844C/T, and -124G/A, respectively) with EGE compared with the control group [26]. The authors concluded the possibility of a combined effect of these polymorphisms on the immune system homeostasis, leading to increased endometrial cell resistance to apoptosis processes [26].

The factors of initiation of programmed cell death also include the ligand of the TNF family that induces apoptosis (TRAIL), which has two types of proapoptotic receptors, TRAIL receptors 1 and 2 [32]. This cytokine is involved in some autoimmune diseases, such as autoimmune thyroiditis and systemic lupus erythematosus [32, 33]. Contrary to reports of a reduced serum TRAIL level in patients with EGE, a study of patients from the Korean population did not reveal a significant role for the polymorphic variants *TRAIL* -49G>A, -615A>G, and -662T>C; *TRAIL-receptor 1* -626G>C; and *TRAIL-receptor* 2 -72T>G in the pathogenesis of EGE [32]. Activation of initiation factors leads to the initiation of apoptosis through the formation of the death-inducing signaling complex (DISC). The main structural link of the DISC is the adaptive protein FADD, which oligomerization is required for the subsequent activation of procaspase-8 in the receptor complex [10]. A 2012 study assessed the expression of *FADD* genes in the endometrial tissue during the implantation window in patients with polycystic ovary syndrome. The researchers reported that decreased characteristics of apoptosis, as well the expression of *FADD*, may explain the decreased endometrial receptivity in this disease [34]. In the literature sources available, no information on the expression of *FADD* genes by EGE was found.

The formation of caspase-8 (CASP8) from the precursor after trimerization of FADD predominantly initiates further signaling of the extrinsic apoptosis pathway. However, in some cases, CASP8 transfers the cascade of reactions along the intrinsic pathway [35]. High expression of CASP8 was detected in samples of the ovarian cortex surrounding the endometriomas (<4 cm in size). Thus, the inferiority of apoptosis in ovarian tissue in patients with endometriosis was confirmed in the absence of an increased expression of factors of the next level, CASP3 and BID/tBID [40]. A 2013 publication showed an association between SNPs (rs1250248) CASP8 and endometriosis; however, its

correlation was weak ($p = 0.049$) [37]. Researches of other CASP8 polymorphisms within the EGE reported no significant association [30].

CASP10, like CASP8, is a factor initiating the extrinsic pathway of apoptosis [12]. Recent studies indicate the ability of some polymorphic variants to lead to dysregulation of apoptosis, which causes oncological diseases [38]. The 2012 meta-analysis results revealed an increased probability of cancer (especially breast cancer) in patients with the rs13006529 T-allele (AT+TT) [39]. Data on the role of CASP10 in the pathogenesis of endometriosis was not presented in the literature over the past 10 years.

CASP3 and CASP7 are considered to be the effector caspases of apoptosis (both extrinsic and intrinsic pathways). The functions of the first factor imply the release of reactive oxygen species and the efficient implementation of the process itself, whereas CASP7 is required for post-apoptotic removal (or "detachment") of a cell from the extracellular matrix [40]. Reduced expression of the CASP3 factor was detected in the endometrium and heterotopies of patients with EGE compared to that of the control group ($p < 0.05$) [41]. Concurrently, the blood serum level of CASP3 was significantly higher in patients with grades III–IV EGE compared to that of the group with grades I–II EGE and in the control group [42]. In addition, the sensitivity of CASP3 determination in the serum of patients with grades III–IV EGE was 90% and the specificity was 87%. These results confirm the impairment of apoptosis processes in endometriosis. The role of the functionally active polymorphisms CASP3 and CASP7 revealed a more frequent prevalence of SNPs CASP3 and CASP7 in patients with endometrial cancer [43]. No works are available in the literature that investigated the SNPs CASP3 and CASP7 in EGE.

In some cases, CASP8 (Figure) activates BID. This factor (a protein of the BCL2 family) is a link between the intrinsic and extrinsic pathways of apoptosis and is considered to initiate mitochondrial damage caused by CASP8 [12]. *BID* gene polymorphisms are widespread among female patients with breast and stomach cancer compared with the control group ($p < 0.05$) [44], but data on the effect of BID SNPs on the occurrence of EGE is unavailable.

Subsequently, activated BID, namely tBID, moves to the mitochondrial membrane and promotes the release of cytochrome C, which is necessary for apoptosome formation [11]. The role of this cytochrome and apoptosome is discussed below within the intrinsic apoptotic pathway.

Intrinsic apoptotic pathway

In the intrinsic pathway (pathway 2), a variety of stimuli that cause cellular stress or damage usually activate one or more members of the BH3 protein family [12]. Activation of BH3 proteins above a critical threshold overcomes the inhibitory effect of antiapoptotic members of the B-cell lymphoma-2 (BCL-2) family and promotes assembly of BCL-2X (Bax) oligomers and BCL-2 antagonist (Bak) within the outer mitochondrial membrane (pore formation).

The outer membrane of the mitochondria under physiological conditions is permeable to molecules weighing up to 5 kDa. During permeabilization (increased permeability) of the outer mitochondrial membrane, pores (MOMPs) are formed, which allow proteins over 100 kDa to pass through [45]. Such pores provide the release of the intermembrane space proteins (Figure), such as cytochrome C and the secondary mitochondrial caspase activator, Smac/DIABLO. The latter neutralizes the inhibition of caspases caused by a family of proteins inhibiting apoptosis (IAP), in particular XIAP. When cytochrome C enters the cytoplasm, it interacts with the APAF, triggering the assembly of the apoptosome, which activates CASP9. Active CASP9, in turn, releases CASP3 and CASP7, which leads to cell death [12].

BH proteins

Bcl-2 family proteins have at least one homologous Bcl-2 (BH–Bcl-2 Homolog) region. These proteins can be classified into three groups. Group 1 contains the antiapoptotic proteins Bcl-xL and Bcl-2, which include all four (BH1–4) domains. Group 2 includes the Bak and Bax apoptotic proteins with three BH domains (BH1, BH2, and BH3). Members of group 3 BH3, which are also apoptosis inducers, have only one domain (BH3). This group includes proteins BID, Bcl-2-interacting killer (BIK), Bcl-2-like protein 11 (BIM), p53 upregulated modulator of apoptosis (PUMA), Bcl-2 modifying factor (BMF), phorbol12-myristate-13-acetate-induced protein 1 (NOXA), Harakiri (HRK), and Bcl-2-associated death promoter (BAD) [11].

Overexpression of proteins containing only BH3 promotes apoptotic death in most cell types but requires the presence of either Bax or Bak factors [46]. These events ultimately lead to increased permeability of the outer mitochondrial membrane and the formation of MOMP.

At the time of publication, no information was found in the sources on the association of polymorphic variants of genes of *BIK*, *BMF*, *HRK*, *and BAD* factors with the development of EGE, thus further research is required. Protein BID, which is also involved in the external cascade of apoptosis activation, was described above.

The expression of the BIM protein in tissue samples of endometriosis-associated ovarian cancer is reduced, as well as in foci of endometriosis located close to cancer cells, compared with the control group [47]. However, we failed to find results in the study of *BID* gene polymorphism in patients with EGE.

Decreased expression of NOXA receptors was determined in the glandular epithelium of female patients with endometrial hypoplasia as a manifestation of apoptosis dysregulation and endometrial receptivity. Therefore, the

authors concluded that incomplete cytotrophoblast invasion occurs [48]. NOXA, like PUMA, is activated in a transcriptional p53-dependent manner. Therefore, DNA damage leads to an increased synthesis of these proteins. Thus, a decreased p53 activity results in impaired activation of the intrinsic apoptotic pathway [12].

The next components in the chain of apoptosis activation processes also belong to the BCL-2 family of proteins, but with three BH domains (BH1, BH2, and BH3). This group includes the proapoptotic proteins Bax, Bak, and Bok, required for MOMP.

Bax is known to increase the susceptibility of cells to apoptosis by inhibiting the BCL-2 factor. The expression of *Bax* informational ribonucleic acid (mRNA) in the endometrium of healthy women increases throughout the cycle, reaching a maximum by the late secretory phase. Data on *Bax* expression in EGE are ambiguous. Numerous studies revealed a significantly reduced expression of the Bax protein in the endometrium of patients with EGE compared with the level of expression in the glandular component of endometrioid cysts and the endometrium of healthy women [49]. Along with a decreased apoptosis in the endometrium of patients with EGE, the mRNA content of the proapoptotic *Bax* gene does not change during the menstrual cycle. Concurrently, recent work by A.A. Delbandi et al. found significant differences between Bax expression in the endometrial tissues and heterotopies in patients with EGE and the endometrium of the control group. This discovery may imply that dysregulation is not a characteristic of all genes involved in the regulation of apoptosis in patients with endometriosis [50].

R. Depalo et al. revealed a significantly low expression of proapoptotic proteins, Bax and Bak, in the ovarian cortical tissue samples from patients with EGE compared with that of the control group. Together with overexpression of the antiapoptotic protein survivin in the EGE group, these results demonstrate a decreased sensitivity of cells to spontaneous apoptosis [51].

A study of the *Bax* and *Bak* genes revealed a significant association between the SNP -284G/A of the *Bax* promoter and breast cancer, which consider this polymorphism as a risk factor for the development of an oncological process [52]. The literature provides no reports on the functionally significant SNPs *Bak* and *Bok* associated with EGE.

The apoptosis system homeostasis is achieved by the antagonistic effect of the last group of proteins BCL-2. BCL-2 and its forms (BCL-XL, MCL1, BCL2A1, BCL-W, and BCL-B) contain four BH domains and block apoptosis. The antiapoptotic proteins BCL-2 prevent the development of apoptosis by preventing BH3-induced oligomerization of proapoptotic Bax and/or Bak members in the outer mitochondrial membranes and subsequent permeabilization [12].

The antiapoptotic proteins BCL-2 bind differently to proteins containing only BH3. Some proteins, including only BH3 (e.g., BID and BIM), interact with almost all antiapoptotic proteins of BCL-2, whereas others (for example, NOXA) interact only with some members of the BCL-2 family, which justifies the peculiarity of their action. Currently, factors BCL2A1, BCL-W, and BCL-B are considered auxiliary in the intrinsic pathway of apoptosis implementation. The sources used do not contain works on their role in the EGE.

The antiapoptotic BCL-2 was established to be necessary for the survival of both glandular and stromal cells. Protein BCL-2 is expressed in glandular cells [49]. The peak level of its expression is registered in the late proliferative phase of the menstrual cycle. The expression of BCL-2 in the myometrium was noted to remain stable throughout the entire cycle. In the endometrium of healthy women, the expression of antiapoptotic BCL-2 is higher in the cells of the basal layer of the endometrium, whereas the expression of proapoptotic Fas and CASP3 is higher in the functional layer cells [53].

BCL-2 is one of the most studied factors of apoptosis. Research results noted the highest level of expression in stromal cells of endometrioid heterotopies, without cyclical changes in the glandular cell expressions. By inhibiting apoptosis, BCL-2 leads to an abnormal ability of cells to survive outside the uterine cavity [51, 54]. A characteristic of ovarian endometriosis consists of a low expression of BCL-2 compared to heterotopies, but a high expression of Bax, which, however, does not lead to a further cascade of cell death reactions [54].

The next antagonist of apoptosis is BCL-XL, in which increased mRNA expression was detected in heterotopies compared to the endometrium of patients with EGE and the control group. Concurrently, the ratio of expression levels for Bcl-xL/Bcl-xS (antiapoptotic/proapoptotic factor) was significantly higher in the endometrium of female patients with EGE compared with the endometrium of women in the control group [54]. The results obtained confirm the high resistance to apoptosis and the survival of endometrial cells in endometriosis.

Cytoplasmatic factors

After permeabilization caused by the BH-3 proteins listed above, cytochrome C and DIABLO migrate into the cytoplasm to activate APAF and form an apoptotic apoptosome and interact with CASP9 [11, 12]. Currently, results were obtained regarding the role of some factors in the pathogenesis of EGE.

Cytochrome C is a pro-apoptotic factor necessary for the formation of an apoptosome. Data are reported on the registration of increased cytochrome C expression when testing some drugs in EGE models as a marker of the apoptosis processes efficiency [55].

O. Leavy demonstrated the absence of APAF1 protein expression in the endometrium in patients with EGE in case of increased expression of estrogen beta receptors [56]. Therefore, assumptions about the suppression of apoptosis in hyperestrogenemia in patients with EGE can be substantiated [15].

A meta-analysis of polymorphic variants of *CASP9* conducted by Z.Y. Zhang et al. revealed that the carriage of the T-allele rs4645981 and the T-allele rs4645981 may increase the risk of cancer, whereas the A-allele rs1052576, A-allele rs1052576, T-allele rs2308941, and T-allele rs2308941 are associated with a decreased disease prevalence [56]. No information was found in the literature on the role of CASP9 in the pathogenesis of endometriosis.

A secondary mitochondrial caspase activator Smac/DIABLO is required to inhibit apoptosis inhibitor proteins (IAPs). The blood serum level of Smac was significantly lower in the group of patients with endometriosis-associated ovarian cancer compared with patients in the control group and EGE patients [58]. Currently, Smac-mimetic drugs are being developed, that block IAPs to treat, first of all, cancer diseases [59].

The family of IAPs is also referred to as direct regulators of the intrinsic pathway of apoptosis.

Proteins of the apoptosis inhibitor family are involved in the suppression of functions of both proapoptotic factors of the BCL-2 family and the effector CASP3, -7, and -9. Eight proteins of the IAP family (NAIP [*BIRC1*], cIAP1 [*BIRC2*], cIAP2 [*BIRC3*], XIAP [*BIRC4*], survivin [*BIRC5*], BRUCE [*BIRC6*], ML-IAP [*BIRC7*], and ILP2 [*BIRC8*]) were identified in people. Overexpression of IAPs protects against several proapoptotic stimuli in malignant diseases [60]. In addition to their participation in the processes of apoptosis, they are also assumed to play a role in cell differentiation, proliferation, and signaling during the immune response, which is impaired in EGE [61].

NAIP (*BIRC5*) and ML-IAP (*BIRC7*) are associated with the transformation of endometrioid cells into carcinoma cells [62]. The available sources report no direct association of SNPs *NAIP* (*BIRC1*), as well as *BRUCE* (*BIRC6*) and *ILP2* (*BIRC8*), with the development of EGE.

The involvement of cIAP1 (*BIRC2*), cIAP2 (*BIRC3*), XIAP (*BIRC4*), and survivin in the pathogenesis of EGE was established by T. Uegaki and A. Watanabe. The authors revealed that the expression of these factors and their mRNA was significantly higher in the foci of endometriosis compared with the endometrium. These results confirm the predominance of antiapoptotic processes in EGE [63].

Local impairment of the mechanisms of apoptosis contributing to EGE foci progression is confirmed by a high level of XIAP (*BIRC4*) expression in samples of the ovarian cortex surrounding endometriomas compared with samples from healthy women in the control group [64]. In addition, the use of XIAP (*BIRC4*) as a biomarker is limited due to the absence of a significant difference in the level of this indicator in the peripheral blood [65].

Survivin is considered a potential biomarker of EGE. Thus, the sensitivity to determine the degree of *BIRC5* mRNA expression in the peripheral blood for the diagnosis of endometriosis was 97.2% and the specificity was 65.5%, taking into account all patients with EGE [66]. As for patients with I–II grades of EGE according to the American Fertility Society (AFS) classification, the method sensitivity was 100% and the specificity was 79.3%, whereas in the group of patients with grade III–IV endometriosis according to the AFS classification, it was 95.8% and 65.5%, respectively. In addition, the sensitivity and specificity for the general group can be increased by additional determination of serum CA-125 level and *Vascular endothelial growth factor* mRNA expression [67].

In 2012, only one study was published about the same SNP distribution of -241C/T ($p = 0.854$), -235G/A ($p = 0.951$), and -31G/C ($p = 0.904$) in patients with endometriosis and the control group [68]. In addition, no differences were found in serum antibody concentrations to survivin between groups, necessitating a further study of this factor.

Caspase-2-dependent apoptosis pathway

Pathway 3 depends on the presence of CASP2, which can be activated by p53 during persistent DNA damage [69]. Double-stranded DNA strand breaks activate kinases that are mutated in ataxia and telangiectasia (ATM) and ATM-associated receptors, which in turn phosphorylate and activate several target proteins, including checkpoint kinase 1 (Chk1) and checkpoint kinase 2 (Chk2). Chk2 activates the p53 pathway, which can lead to cell cycle arrest and activation of DNA-dependent protein kinase (DNA-PK) [69]. In severe damage, DNA-PK forms a complex with the P53-induced protein containing the death domain (PIDD) and procaspase-2. This complex (PIDDosome) phosphorylates and activates CASP2. Activated cytosolic CASP2 cleaves BID to tBid, which induces MOMP, activates CASP9 and CASP3, and ultimately apoptosis [70].

Among the participants in this mechanism of apoptosis, CASP2 and its putative role in the control of the number of oocytes, as well as the p53 factor, are noted [69, 71].

The result of P53 activation is the arrest of the cell cycle and DNA replication, and under severe stress, the initiation of apoptosis. This factor has ample opportunities for inducing apoptosis processes in addition to the "own" CASP2-mediated method, namely through an external cascade by interacting with the Fas and TRAIL factors, as well as with the help of BCL-2 proteins (Bax, NOXA, PUMA, and BID) [71].

A decreased expression of *p53* mRNA in heterotopic samples compared to expression in the endometrium of

healthy women was emphasized in many studies [64, 72]. However, data on functional polymorphisms of the TP53 promoter are ambiguous. Most researchers found no connection between endometriosis and *TP53* Glg11Lys and *TP53* Arg248Trp-Gln polymorphisms [73]. In addition, original studies and a 2015 meta-analysis demonstrated that *TP53* Arg72Pro increases the risk of EGE in various populations [74]. Nevertheless, researchers on population samples from India do not confirm this assumption [75]. Data on the association of the 16 bp duplication polymorphism in the *TP53* gene and EGE susceptibility were obtained [76]. The current situation necessitates further studies with larger samples.

Granzyme-mediated (caspase-independent) pathways of apoptosis

Apoptosis can also be triggered by direct activation of CASP3 by granzyme B (GZMB). Finally, DNA fragmentation caused by granzyme A (GZMA) can also lead to programmed cell death [77].

The preproprotein encoded by the *GZMA* genes are secreted by natural killer cells and cytotoxic T-lymphocytes and, after proteolysis, form active proteases that induce target cell apoptosis. These proteins also stimulate the synthesis of cytokines and the destruction of extracellular matrix proteins, promoting both the processes of chronic inflammation and repair [78].

Currently, a minor study in 2020 was performed to determine the expression of the *GZMB* gene in the peripheral blood, as well as the SNP (s8192917 G>A) in patients with EGE and the control group. The *GZMB* level was higher in patients with the GG genotype; however, the differences were insignificant [79].

CONCLUSION

Therefore, this review considers the main stages and participants in the processes of apoptosis from the viewpoint of their possible role in the pathogenesis of endometriosis.

Over the years, great progress has been made in uncovering the molecular basis of apoptosis. Further study of these processes is necessary to understand the details of cell coordination and the formation of a response to their destruction. The formation of such an impaired reaction is possible to be the principal in the study of not only apoptosis but also related diseases, such as EGE. The review presented the study results over the past 10 years and focused on the analysis of polymorphic variants of genes regulating apoptosis in EGE. Endometriosis is a common multifactorial disease resulting from interactions between multiple gene loci and the environment. A broad analysis of genes involved in the complex regulatory system of apoptosis can lead to the identification of factors of disease predisposition, as well as a better understanding of the etiology and possibility of predicting its course.

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