Inflammation and ovarian cancer – current views

Rak jajnika i proces zapalny – współczesne poglądy

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Abstract

Ovarian cancers pose the greatest challenge for gynecological oncology. They are a heterogeneous, rapidly progressing and highly lethal group of malignancies and their etiology is still poorly understood.

Among many hypotheses, explaining the pathogenesis of malignant tumors, chronic inflammation seems to play a significant role, which was proved in cervical, hepatic and esophageal cancers. The processes of inflammation and carcinogenesis are very much alike. Their similarity was experimentally confirmed by epidemiological, immunological, biochemical and genetic studies.

Additionally, this view is supported by indirect epidemiological and clinical evidence linking ovarian cancer with pelvic inflammatory disease, endometriosis or polycystic ovary syndrome. Chronic inflammation is a key factor in the pathogenesis of these illnesses. Moreover, ovulation involving repeated damage and repair of the ovarian surface epithelium is in fact an inflammatory process.

In this review, we focus on the role of inflammation in cancer initiation, promotion and progression with special emphasis on the ovarian cancer. We discuss the potential involvement of the fallopian tubes, endometriosis and microenvironment of tumors represented by cytokines, chemokines, growth factors and various enzymes that destroy the extracellular matrix. Considering that molecular biology is currently rapidly evolving, we focus on the function of the mammalian target of rapamycin (mTOR) kinase and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) in the pathophysiology of inflammation and cancer.

Key words: **ovarian cancer** / **fallopian tube cancer** / **inflammation** / **endometriosis** / / **carcinogenesis** /

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Streszczenie

Nowotwory jajnika są największym wyzwaniem w onkologii ginekologicznej. Stanowią heterogenną, gwałtownie postępującą oraz wysoce śmiertelną grupę guzów, których etiologia ciągle jest w znikomym stopniu poznana.

Wśród wielu hipotez wyjaśniających patogenezę nowotworów przewlekłe zapalenie wydaje się odgrywać zasadniczą rolę, co udowodniono w przypadku raka szyjki macicy, wątroby czy przełyku. Stan zapalny i kancerogeneza to w istocie bardzo podobne do siebie procesy, zostało to doświadczalnie potwierdzone na gruncie epidemiologii, immunologii, biochemii czy genetyki. Pośrednich dowodów, iż rak jajnika związany jest z przewlekłymi procesami zapalnymi dostarczają dane epidemiologiczne i kliniczne wiążące ten nowotwór z PID (stan zapalny narządów miednicy mniejszej) endometriozą czy zespołem policystycznych jajników. W etiologii tych schorzeń stan zapalny odgrywa dominującą rolę.

Dodatkowo proces owulacji polegający na cyklicznym uszkadzaniu i odtwarzaniu nabłonka pokrywającego jajnik ma w istocie podłoże zapalne.

W naszej pracy skupiliśmy się na roli jaką proces zapalny odgrywa w inicjacji, promocji i progresji nowotworów ze szczególnym uwzględnieniem raka jajnika. Omówiona została potencjalna rola jajowodów, endometriozy oraz mikrośrodowska guza reprezentowanego przez cytokiny, chemokiny, czynniki wzrostu czy enzymy niszczące macierz pozakomórkową. Szczególną rolę położono na intensywnie rozwijające się badania molekularne i rolę kinazy mTOR oraz czynnika transkrypcyjnego NF-kappaB.

Słowa kluczowe: **rak jajnika** / **rak jajowodu** / **zapalenie** /**endometrioza** / / **karcynogeneza** /

Introduction

Ovarian cancers are the second (after endometrial cancer) most common group of gynecologic cancers. According to the data reports from the National Cancer Registry, there were 3474 new cases of ovarian cancer in Poland in 2009. Therefore, it is the sixth most common malignancy among women following breast, lung, colon, skin and endometrial cancer with an estimated 204 000 new cases and 125 000 deaths per year worldwide [1].

The five-year survival rate for ovarian cancer is as low as 30%, consequently, it is one of the leading causes of cancer deaths among women [2]. The most common ovarian cancer arises from the ovarian surface epithelium. It is estimated, that approximately 90 to 95% of all ovarian malignancies are epithelial cancers. The development of cancer from the ovarian epithelium explains the strong tendency to early peritoneal spread and ascites [3]. There are many theories explaining the pathogenesis of ovarian cancer, including the chronic inflammation, which seems to play a significant role. Despite extensive scientific research in this field, molecular mechanisms correlating carcinogenesis and inflammation, are still poorly understood.

Pathogenesis of ovarian cancer

A number of theories have been proposed to explain the causes of ovarian cancer. The most widely accepted is the Fathalla's 'incessant ovulation' hypothesis with repeated damage of the ovarian surface epithelium [4]. The known risk factors of ovarian cancer – nulliparity, early menarche, late menopause and the use of hormonal contraceptive pills (reducing the incidence of this disease), support the Fathalla's theory. The ovulation process is accompanied by formation of ovarian inclusion cysts containing surface epithelial cells. These cells are exposed to various autocrine and paracrine agents such as hormones, phospholipids eicosanoids and cytokines exerting stress and causing damage.

Another theory assumes proliferative and mutagenic influence of high levels of gonadotropins during ovulation and in postmenopausal women [5]. Proliferative effect of androgens and progesterone may also contribute to the development of this disease [6].

Inflammation and carcinogenesis

Acute inflammation is a protective tissue response to injury or destruction, which serves to destroy the injurious agent and heal injured tissues. Under normal physiological conditions it resolves spontaneously after restoring the tissue architecture and function. Various pathological states such as persistent infection or immunological deficiency can lead to chronic inflammation, resulting in tissue injury and carcinogenesis. The possible relationship between inflammation and cancer was first mentioned in 1863 by Rudolf Virchow. He observed the infiltration of leukocytes in neoplastic tissues. Over half a century later, Harold Dvorak made a hypothesis, that the basic developmental mechanism of both, inflammation and carcinogenesis, is angiogenesis and that tumors are "wounds that do not heal". Chronic inflammation has been proven to be a key factor in pathogenesis of various malignancies, such as primary liver cancer resulting from hepatitis C virus infection, esophageal cancer and Helicobacter pylori infection or cervical cancer and human papillomavirus infection. Growing body of evidence supports the theory that non-steroidal anti-inflammatory drugs (NSAIDs), especially aspirin, protect against cancer [6].

The developmental mechanisms of inflammation and carcinogenesis are very complex. Inflammation influences all stages of cancer formation i.e. initiation, promotion and progression. Various inflammatory mediators participate in the formation of cancers acting as growth factors or angiogenic factors. There are many potentially effective anticancer drugs directed at pro-inflammatory cytokines, such as, IL-6 or TNF-α. Moreover, reactive oxygen species (ROS) along with reactive nitrogen species (RNS) greatly contribute to carcinogenesis by inducing a cellular redox imbalance which has been found in various cancer cells [8].

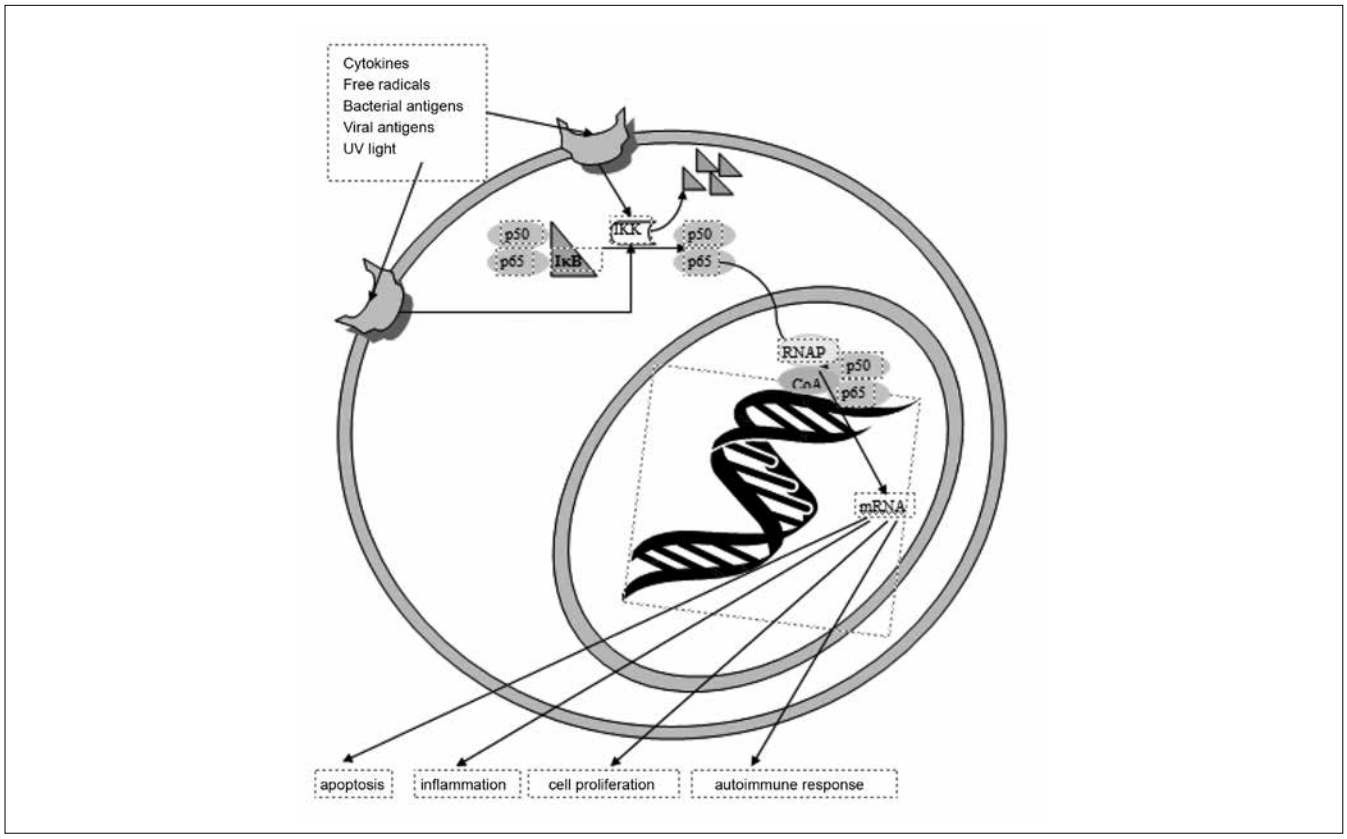

Figure 1. NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex. It controls transcription of DNA and plays an important role in inflammation, autoimmune response, apoptosis and cell proliferation. NF-κB can be found in almost all eukaryotic cells. It is homo- or heterodimer of different subunits, in this case p50 and p65. In the cytoplasm of unstimulated cells NF-κB is bound to regulatory proteins called inhibitors of κB (IκB). Stimulation of cells leads to proteolytic degradation of IκB by the enzyme IκB kinase (IKK) and therefore activation of NF-κB. After translocation into the nucleus, NF-κB forms a complex with RNA polymerase (RNAP), coactivators (CoA) and DNA. The complex leads to transcription of DNA to mRNA..

The significance of immune system in the formation of cancer is still poorly understood. On one hand, the immunosuppression enables the cancer cells to evade detection, and on the other, the immune system forms a barrier against carcinogenesis. The most recent research, has provided evidence, that many genes involved in the development of cancer show activity in the inflammatory processes. They act as modulators of immune response in the way that facilitates the formation of cancer.

Inflammation and ovarian cancer

Ovarian cancer arises mainly from the ovarian surface epithelium. Due to the specific location of the ovarian epithelial cells in the peritoneal cavity they are distinctly exposed to various pro-inflammatory agents. There are various sources of this type of inflammation. It has been found that ovulation itself is a process of potentially inflammatory and mutagenic character [7]. During ovulation, epithelial cells in the immediate vicinity of the ovarian follicle undergo extensive proliferation, destruction and apoptosis, resulting in the rupture of the follicle wall and subsequent remodeling and repair. It is postulated that this sequential course of action causes oxidative stress through increased concentration of pro-inflammatory mediators such as cytokines, interleukins, growth factors, prostaglandins and eicosanoids [8]. Another factor which links ovulation, inflammation, tumor growth and spread is the activity of collagenases, enzymes that destroy the extracellular matrix. The repeated cycles of cellular damage and repair in highly oxidative environment favor errors during DNA replication. In patients with ovarian cancer, the peritoneum, covering most of the intra-abdominal organs, shows macroscopic manifestations typical of inflammation such as swelling, redness, increased density of blood vessels, adhesions or ascites [7]. Ovarian cancer risk is positively associated with increasing serum levels of CRP which further supports the theory relating ovarian cancer to chronic inflammation [9]. Previously mentioned preventive influence of NSAIDs depends on the suppression of transcription factor NF-kappaB. It is a protein complex that controls the transcription of DNA and plays a key role in controlling the immune response to infection as well as cell proliferation and survival. The increased activity of NF-kappaB is observed in both, the inflammatory states and a considerable percentage of all cancers. NF-kappaB inactivation leads to lower concentration of growth factors, adhesive molecules, apoptosis regulators, cytokines and chemokines (COX-2, VEGF, IL-8/CXCL8, MCP-1/CCL-2, MIP1alpha/CCL-3, tPA and Upa), which suppresses angiogenesis, invasion and resistance to apoptosis [7] (Figure 1). Techniques aimed at the inactivation of NF-kappaB are successfully used in the treatment of chronic inflammatory diseases and are a promising direction in the treatment of cancer [10].

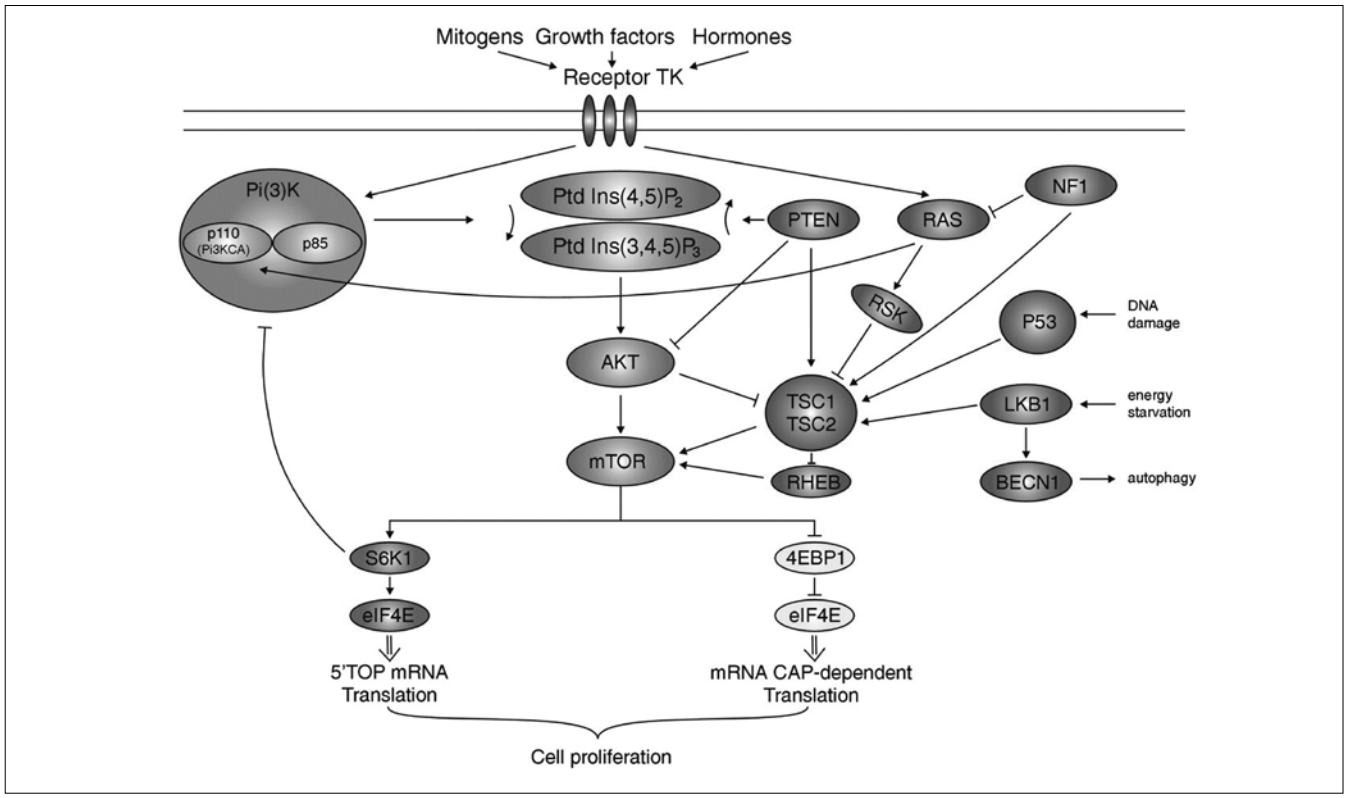

Figure 2. Conserved seronine/threonine kinase mTOR integrates the input from upstream pathways, including mitogens, growth factors and hormones. mTOR enhances translation initiation in part by phosphorylating two major targets: the 4E-BP1 (inhibitory 4E-binding protein) family of proteins and ribosomal protein S6 kinases (for example oncogene S6K1). By phosphorylating the 4E-BP1, a well established tumor suppressor, mTOR represses its capacity to inhibit the mRNA cap-binding protein transcription factor eIF4E - a known potent oncogene. Translation is also prompted by activated S6K1, which co-operates to regulate gene expression and translation processes, particularly the translation of proteins encoded by 5'terminal oligopyrimide (5'TOP) genes. On the other hand, activation of AKT is physiologically prevented by a gene product of tumor suppressor PTEN (phosphatase and tensin homologue deleted from chromosome 10), a phosphatase that removes the phosphate attached by PI3K from PIP3. AKT protein is also an indirect positive regulator of mTOR through the phosphorylation and inactivation of mTOR inhibitors, such as protein products of the TSC1 and TSC2 genes - well established tumor suppressors. Tumor suppressor genes LKB1, p53, NF1 also, albeit indirectly regulate the activity of mTOR.

Ovarian and fallopian tube cancer

Pathology findings in reviewed specimens from BRCA mutation carriers after prophylactic and risk-reducing salpingo-oophorectomy revealed precursor lesions and foci of highly differentiated serous carcinoma in fallopian tubes [11, 12]. These changes were almost exclusively located in the distal or fimbriated end of the fallopian tube [13]. This observation leads to a conclusion that at least some percentage of the highly malignant ovarian cancers may originate from the fallopian tubes. These structures are the point of contact for ciliated columnar epithelium lining the lumen of the uterine tubes and mesothelium covering the peritoneal cavity. The site of their contact is especially prone to inflammation and damage, which was confirmed in the case of cervical and esophageal carcinoma [14]. Oviduct is an organ particularly liable to inflammation. Pathogens most frequently found here are *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma hominis*, as well as other aerobic and anaerobic bacteria [15]. Adnexitis has been proven to be one of the causative factors of ovarian cancer [16]. Authors assessed the risk of ovarian malignancy in a group of patients with pelvic inflammatory disease to be 2.78 per 10,000 person-years, as compared to an incidence of 1.44 per 10,000 person-years in patients from the control group. They also found, that the hazard ratio was highest among women who have had multiple episodes of PID. Chemicals such as asbestos or talc commonly used for intimate hygiene also contribute to fallopian tube damage and cell transformation [17]. One of the most significant factors repeatedly irritating the epithelial lining of the uterine tubes is a retrograde flow of menstrual blood, rich in particles having oxidative properties such as heme and iron [18]. This mechanism is the most widely accepted theory explaining the pathogenesis of endometriosis, uterine tubes inflammation and cancer. Chronic inflammation is often observed in the oviducts surgically removed from patients with ovarian cancer [19]. In the study by Seidman *et al.,* 50% of fallopian tubes removed from women with ovarian malignancy showed inflammation, as compared with 27% obtained from noncancerous patients. The protective effect of hysterectomy provides further, albeit indirect, evidence that retrograde spillage of menstrual blood plays an important role in the ovarian carcinogenesis [20]. These observations lead to a conclusion, that during removal of the uterus performed due to benign conditions such as myomas, in patients wishing to retain ovaries, bilateral salpingectomy should be considered in order to lower the risk of ovarian carcinoma.

Ovarian cancer and endometriosis

Endometriosis is a chronic, benign inflammatory disease, affecting millions of women of reproductive age throughout the world. There is a great amount of epidemiological and histological data linking the incidence of this disease with endometrial and ovarian clear cell carcinoma [21]. The group of endometriosis-associated ovarian cancers (EAOC) is characterized by relatively low malignant potential and high detection rate in their early stages. It was demonstrated, that the uninterrupted menstrual cycle is a common risk factor for endometriosis and ovarian carcinoma [22]. Chronic inflammation and sex hormones acting via autocrine or paracrine mechanisms, seem to play a crucial role in carcinogenesis [23]. A broad spectrum of cytokines, growth factors and/or matrix metalloproteinases released with the occurrence of endometrial lesions stimulate mitotic activity, angiogenesis, growth, differentiation, migration and apoptosis [24, 25]. The inflammatory milieu favors genetic modifications of ectopic endometrial implants, which may eventually lead to cancer. Molecular analysis of endometrial and neoplastic tissues confirmed the presence of similar genetic abnormalities in both endometriosis and ovarian carcinoma. Among them, loss of heterozygosity (LOH) on chromosomes 1p, 9p, 1lq, 17p and 22q, amplification at 17q, mutations of oncogenes (e.g. *K-ras*) and PTEN tumor suppressor genes, as well as overexpression of selected genes related to mammalian target of rapamycin (mTOR) pathway are detected [26, 27]. Mutation of *p53* suppressor gene is one of the most frequently encountered aberration in endometrial and neoplastic tissues. Disturbed function of *p53* results in excessive cellular proliferation and inhibition of apoptosis. Kinase mTOR plays a important role in pathogenesis of ovarian cancer and endometriosis, and is responsible for regulation of cell proliferation and growth. High activity of mTOR, especially in postmenopausal women, was confirmed by analysing specimens taken from endometrial lesions and ovarian cancer [28]. This protein integrates the input from upstream pathways including hormones, growth factors, mitogens and nutrients. Interactions between various oncogenes and tumor suppressor genes are shown in Figure 2. Kinase mTOR inhibitors are successfully applied as immunosuppressive agents. Ongoing scientific research will explain whether these drugs are beneficial in the treatment of tuberous sclerosis and cancer. The efficacy of temsirolimus, an mTOR/AKT inhibitor, was confirmed in the successful treatment of deep infiltrating endometriosis in mice, and therefore, it may offer a promising therapy to be applied in humans [29].

Summary

Malignant neoplastic diseases remain one of the greatest challenges in the twenty-first century science. Despite the immense progress in medicine over the recent years their pathophysiology remains unclear in many aspects and calls for even more efforts. Among many factors contributing to cancer development, chronic inflammation seems to play a significant role. Understanding these processes will result in the introduction of new therapies improving the outcomes of treatment.

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