REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Interleukins (IL-1A and IL-6) and the risk of Endometrial Carcinoma

Asmaa Ramadan [a*], Reda Hemida [b], Eman T. Mehanna [c], Dina M. Abo-Elmatty [c]

[a] Biochemistry Department, Faculty of Pharmacy, Delta University for Science & Technology, International Coastal Road, Gamasa City, Mansoura, Dakhliya, Egypt; [b] Obstetrics and Gynecology Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt; [c] Biochemistry Department, Faculty of Pharmacy, Suez Canal University, Ismailia, Egypt.

Received: 14. 10. 2022

Revised: 15. 10. 2022

Accepted: 16. 10. 2022

*Correspondence Author:

Tel: +20502944607

E-mail address:

drasmaaismail@gmail.com

Abstract

Endometrial carcinoma (EC) is a cancer that develops in the uterine or womb lining (Endometrium). It is the outcome of cells that have the capacity to move to other parts of the body growing abnormally. Hereditary causes account for 2–10% of all EC cases. Endometrial carcinoma develops as natural endometrial cell development is disrupted, new cells form unnecessarily, and old or weakened cells do not die when they should. The buildup of extra cells sometimes results in the formation of a mass of tissue known as a growth or tumor. This abnormal cancer cells have a number of genetic abnormalities that allow them to proliferate uncontrollably. Interleukins (ILs) are a subset of a larger group of cellular messenger molecules called cytokines, which are modulators of cellular behavior. Interleukins have role in therapeutics as well as diagnosis and prognosis as biomarker in various conditions. Additionally, it has been proposed that genetic polymorphisms in functionally important genes may be risk factors for the development of a number of malignancies, including endometrial cancer. This review pays attention to understand the risk of EC, and the importance of the effect of gene polymorphism (IL-6 rs1800795, and IL-1A rs1800587) on it. Also, their involvement in the etiology, pathogenesis, and outcome of the disease are explained, aiming to provide new insights into the pathogenesis of EC and the possibility to develop novel therapeutic approaches through targeting these genes.

Keywords: Endometrial carcinoma; IL-6; rs1800795; IL-1A; rs1800587.

1. Introduction

Endometrial carcinoma (EC) is described as the unchecked and disorderly growth of certain irregular cells from the endometrium lining, and is therefore classified as a gynecologic cancer. Ageing, dietary imbalances that contribute to obesity, and nulliparity are the major risk factors for EC **(Vălu et al., 2017)**.

Endometrial carcinoma is the most common gynecologic cancer in high-income countries, and it is the sixth most prevalent diagnosed cancer in females worldwide, responsible for both high- and low-income countries (**Bray et al., 2018; Wang et al., 2020)**. Endometrial carcinoma is a gynaecological malignancy that is becoming more and more problematic **(Morice et al., 2016)**. According to the GLOBOCAN cancer statistics, there are an estimated 382,069 new cases diagnosed each year among whom around 90,000

women die from this disease worldwide **(Brüggmann et al., 2020)**. Endometrial carcinoma is the fourth most prevalent type of cancer in women, and the second most common type in developing countries **(Jemal et al., 2011; Torre et al., 2015; Bray et al., 2018)**.

Egypt and South Africa have the highest rates of EC in Africa **(Brüggmann et al., 2020)**. According to Globocan, corpus uteri cancer is the tenth most prevalent type of cancer in Egyptian women. According to the Middle East Cancer Consortium (MECC) Report, when compared to other Middle Eastern nations, Egypt has the lowest incidence rate of uterine cancer (3.5/100,000). Additionally, compared to other female cancers in Egypt, EC has a low stage upon diagnosis **(Alshahrani et al., 2018)**. In the most recent statistic in Egypt, EC represented 1.3% of newly diagnosed cancers in Egypt with 1694 new cases **(GLOBOCAN, 2020)**.

2. Pathogenesis and Risk Factors

Risk factors are qualities that raise the possibility of contracting a disease. Age, ethnicity, the metabolic syndrome, exposure to estrogen without protection, and genetic predispositions to EC are the most important risk factors in the case of EC.

2.1. Age

The majority of EC patients are postmenopausal women, who are diagnosed at an average age of 60 **(American Cancer Society, 2022)**. The peak age-specific incidence occurs between the ages of 75 and 79, with only 5% of patients are younger than 40, with 85% of patients occurring beyond the age of 50 **(Passarello et al., 2019)**.

2.2. Race

The race of a woman appears to be important in the progression of EC, with frequency highest in North America, Northern Europe, Asia and Africa and lowest in Eastern Europe and Latin America **(Burke et al., 2014)**.

2.3. Metabolic Syndrome

A group of risk factors known as metabolic syndrome has been related to a higher risk of diabetes, heart disease, stroke, and other major health issues. Among the risk factors for metabolic syndrome are high blood pressure, high triglycerides, low HDL cholesterol, central obesity, and high blood sugar **(Burke et al., 2014)**.

2.4. Unrestricted Estrogen Exposure

Continued exposure to estrogen without progestin resistance is a risk factor for EC. Estrogen exposure can occur in both endogenous and exogenous forms. Hormone replacement therapy is an example of exogenous estrogen exposure. Chronic anovulation, estrogen-producing tumors, and obesity can all cause endogenous estrogen exposure which leads to EC **(Passarello et al., 2019)**.

3. Tumor markers in endometrial carcinoma

Tumor markers must be recognized for early EC detection in order to enhance prognosis. Due of a rise in EC incidence and mortality, tumour markers will be utilised to direct therapy, monitor treatment effectiveness, and foretell recurrence. Tumor markers are molecules that can be discovered in malignant cells, urine, or blood. Recently, for diagnostic or prognostic purposes, In EC, no particular tumour markers with high specificity and sensitivity have been found **(Aksel and Çakir, 2020)**.

3.1. Human Epididymis Protein

Human Epididymis Protein (HE4) is located on chromosome 20 at 20q12–13 which present in the respiratory and the epithelium of reproductive tract. It is significantly expressed in several cancer tissues. It has been accepted as a novel tumour marker for epithelial ovarian cancer by the US Food and Drug Administration (FDA). Numerous studies are looking into HE4 as a marker because EC and ovarian cancer are so similar. HE4 expression in serum and tissue is a sensitive, specific diagnostic, and predictive biomarker in endometrial cancer **(Mohammad et al. 2022)**.

Additionally, it helps forecast disease stage and extrauterine involvement. The results of **Cuesta-Guardiola et al. (2021)** about the usefulness of HE4 are in contrast to those of prior studies. They found that both cancer patients and healthy control had poor tissue HE4 correlation. The positive serum test results show that the tumour marker HE4 seems to be able to recognise EC. In a recent meta-analysis, it was discovered that patients with

EC who had high HE4 concentrations had shorter survival times **(He et al., 2020)**. According to **Angioli et al. (2016)**, the HE4 cutoff value can be used to categorize patients as having a high or low risk of developing EC again.

3.2. Cancer Antigen 125

The peritoneum, pleura, and pericardium, as well as tissues made of cholemic epithelium including the endocervix, endometrium, and tubes, are examples of tissues that contain the glycoprotein known as cancer antigen 125 (CA-125). Epithelial ovarian cancer is frequently diagnosed with the tumour marker CA-125 when equal to 35 U/mL and this is considered to be the acceptable serum cutt-off value. In addition to normal physiological conditions like pregnancy and the menstrual cycle, benign pathological disorders including endometriosis, pelvic infection, and uterine fibroids can cause an increase in CA-125 levels **(Aksel and akir, 2020)**.

Additionally, there are studies that support the use of CA-125 in EC diagnosis. According to a recent study, ECs' patients had higher levels of CA-125 than healthy controls. Additionally, they showed that CA-125 had a 52.6% sensitivity and an 80% specificity for EC detection **(Nithin et al., 2018)**. CA-125 preoperative serum in a cohort of 393 patients with EC, greater than 27.6 U/mL continued to be an independent risk factor for metastatic lymph node of the pelvic, and a rise in CA-125 was discovered to be a risk factor as well **(Li et al., 2019)**.

According to **Kotowicz et al. (2017)**, serum levels of CA-125 were higher in stage I-Ib EC patients in comparison to to healthy controls, and levels of CA-125 were also greater in patients with metastatic lymph node in comparison to those without lymph node metastasis **(Kotowicz et al., 2017)**.

3.3. Cancer Antigen 19-9

In general, cancer of stomach, lung, and ovary have higher serum levels of the cancer antigen CA 19-9 (CA 19-9), although some investigations have found that EC cases also had higher CA 19-9 levels. 22-24% of EC patients had elevated CA 19-9 levels **(Ueda et al., 2010)**. Studies have revealed a correlation between grade and FIGO stage and the elevation of CA 19-9 serum levels **(Bian et al., 2017)**.

3.4. Carcinoembryonic Antigen

A general gastrointestinal tumour marker called carcinoembryonic antigen (CEA) may rise in EC. 14-22% of EC have high levels of CEA. Although there was a substantial difference in serum CEA levels between those with liver and lung metastases, CEA levels were insufficient for EC diagnosis and follow-up **(Aksel and Çakir, 2020)**.

3.5. YKL-40

Tyrosine (Y), lysine (K) and leucine (L) (YKL)-40 is a glycoprotein secreted by inflammatory and cancer cells that can be involved in angiogenesis and cell proliferation in cancer cells. It is also known as Chitinase-3-like protein 1 (CHI3L1). YKL-40 has been linked to an increase in cancers such as colorectal, breast, and lung cancer. Previous research has emphasised that serum YKL-40 levels rise in EC and can be used as a tumour marker in EC **(Cheng et al., 2014; Kemik et al., 2016)**.

In comparison to the control group and patients with progression-free survival, EC patients had greater YKL-40 levels. Additionally, YKL-40 positive patients had lower overall survival rates than YKL-40 negative patients. They also stressed how YKL-40 might be used to actively diagnose and monitor EC patients **(Fan et al. 2013)**.

3.6. Serum Amyloid A

High-density lipoprotein called serum amyloid A (SAA), which is mostly released by the liver, is crucial for both acute and chronic inflammatory processes. A recent meta-analysis study found that solid tumours with high SAA levels have a worse prognosis (Lin et al., 2019).

Cocco et al. (2009) informed the first proof that uterine serous papillary carcinoma (USPC) patients' serum contains significant levels of SAA. Additionally, they demonstrated that in USPC patients, raised levels of SAA before operations can be helpful in expecting a more advanced stage as well as in diagnosing recurrence and treatment response **(Cocco et al., 2009)**. Then, in 2010, they showed that endometrial endometrioid adenocarcinoma (EEC) cells expressed high quantities of SAA, leading to higher levels of SAA in the blood and a significant difference of SAA concentrations between EEC patients and healthy and benign disease participants were found. Additionally, they showed that grade 3 EEC patients' SAA levels are substantially greater than those of grade 1 and 2 patients **(Cocco et al.,**

2010).

Finally, **Omer et al. (2013)** found that blood SAA levels in patients with advanced EC were higher than those in healthy controls. The cutoff threshold for this study was 8.8 U/mL, which had a sensitivity of 68.7% and specificity of 58.6%. To plan the patient's best course of therapy and for preoperative assessment, this cutoff value may be useful.

3.7. Neutrophil Gelatinase-Associated Lipocalin

A secretory protein with numerous biological effects, lipocalin-2, also known as neutrophil gelatinase-associated lipocalin, is crucial for immunological and inflammatory responses, tubular epithelial morphological change, and cancer **(Yu et al., 2014)**.

Although it has been demonstrated that lipocalin-2 is presented in ovarian, colorectal, stomach, and breast malignancies, its effects on the endometrium are still poorly understood **(Aksel and akir, 2020)**. Insulin resistance is controlled by lipocalin-2, which also takes part in the development of cancer. It has a connection to obesity, a risk factor for EC **(Cabia et al., 2016)**. According to **Cymbaluk-Poska et al. (2017)**, EC patients have greater levels of lipocalin-2 expression than healthy endometrium and benign endometrial lesions.

Additionally, it was discovered that grade 3 tumours and advanced stages had greater levels and expression of lipocalin-2, which was linked to lymphovascular invasion and metastatic lymph node **(Cymbaluk-Poska et al. 2017)**. **Cymbaluk-Płoska et al. (2019)** conducted a second investigation on 123 individuals with a BMI more than 21 kg/m2, which demonstrated a correlation between an increase in lipocalin-2 concentration and higher clinical EC staging. They also demonstrated that the lipocalin-2 cutoff serum level that separates benign endometrial alterations from EC is 160 ng/ml. For all women, lipocalin-2 sensitivity (84%) was greater than that of HE4 (66%) and CA125 (52%).

The scientists concluded that lipocalin-2 may act as a helpful biomarker in the early detection of the EC due to its high sensitivity and comparable specificity to HE4 **(Cymbaluk-Płoska et al. 2019)**.

3.8. Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) is involved in a variety of physiological and pathological processes, like cancer, ocular neovascular disorders, wound healing, and embryogenesis. Many different cancer forms, including lung, breast, colon, and melanoma, were shown to have higher VEGF levels **(Mahecha and Wang, 2017)**.

Numerous studies showed that VEGF is connected to EC stage, myometrial invasion, metastasis to lymph node, and degree of differentiation **(Cai et al., 2017; Xu et al., 2018)**. When VEGF levels in two forms of pathologic EC were examined, Type II of EC, but not Type I, VEGF levels was found to be linked with stage **(Soufla et al., 2013)**.

4. Interleukins

Interleukin, a type of cytokine that was previously considered to exclusively be produced, are known that a variety of the cells can create them. They are necessary for the maturation, proliferation, adhesion, migration, and differentiation of immune cells. Additionally, they also possess pro- and anti-inflammatory effects. Interleukins' main role is to regulate growth, differentiation, and activation during inflammatory and immunological processes. Interleukins interact with high-affinity receptors on cell surfaces to trigger a range of reactions in cells and tissues. They regulate both autocrinely and paracrinely. The synthesis of interleukin is a self-limited method. Most interleukins are encoded by messenger RNA, which is unstable and results in a temporary synthesis. Once interleukins were manufactured, these molecules are secreted quickly **(Zeng et al., 2020)**.

4.1. Interleukin-6

In 1986, interleukin-6 (IL-6) was discovered as a B cell stimulatory factor that initiates IgG production. It was later discovered to be a multifunctional cytokine that regulates a variety of biological processes such as organ development, acute-phase responses, inflammation, and immune responses **(Hirano, 2021)**. Human IL-6 is composed of 212 amino acids, including a 28- amino-acid signal peptide, and its gene has been located on chromosome 7p21; accounts for the size of 21–26 kDa of natural IL-6 **(Yang et al., 2022)**.

4.1.1. Interleukin-6 in endometrial carcinoma

Interleukin-6 is a multifunctional cytokine that

plays a role in modulating the expression of cancer **(Masjedi et al., 2018)**. IL-6 is known to promote the proliferation, invasion, and differentiation of trophoblast cells in the normal uterine epithelium. Trophoblast cells in the developing embryo secrete IL-6 on a regular basis. IL-6 is also involved in the promotion of tumour growth **(Cai et al., 2019)**.

Endometriosis is a significant cause of morbidity and is associated with infertility and pain. The three pro-inflammatory cytokines IL-1, IL-6 and tumor necrosis factor (TNF)-alpha, are all involved in the development of endometriosis. Their concentration in the peritoneal fluid is associated with the degree of adhesions present **(Juo et al., 2009)**.

In physiological conditions, IL-6 regulates immune and inflammatory responses; however, recent reports suggested that IL-6 expression is involved in the stimulation of tumour growth and metastatic spread, including breast cancer and other gynaecological tumours. IL-6 levels in prostate cancer patients correlate with the extent of disease and may be monitored in conjunction with other disease markers. IL-6 has also been linked to the progression of uterine cancer **(Drygin et al., 2011; Cai et al., 2019)**.

Interleukin-6 was found in EC cells and promoted cancer progression in a paracrine manner. It was also discovered that IL-6 activation was linked to EC development by inducing aromatase expression in intratumoral stromal cells. IL-6 is known to promote the proliferation, invasion, and differentiation of trophoblast cells in normal uterine epithelium. Trophoblast cells in the developing embryo secrete IL-6 on a regular basis. IL-6 also plays a role in the promotion of neoplastic change. Additionally, IL-6 plays a growth promoting role in tumour growth and metastasis. IL-6 has also been linked to the progression of uterine cancer **(Cai et al., 2019)**. Notably, 17β-estradiol (E2) upregulated IL-6 expressions in endometrial cancer **(Che et al., 2014)**.

In EC patients, high levels of IL-6 were found to negatively correlate with overall survival **(Bellone et al., 2005)**. IL-6 is secreted upon tissue injury and stress. Although innate immune cells represent the major IL-6 source within the tumor microenvironment, tumor cells were also shown to express IL-6 in autocrine fashion. Upon its secretion, IL-6 binds to its receptor (IL-6Rα or CD126). CD126 encompasses a short cytoplasmic domain that interacts with the expressed second transducer glycoprotein 130 (GP130). Binding of IL-6 to CD126 and their association with GP130 triggers the activation of Janus kinases (JAK), which phosphorylate Signal transducer and activator of transcription 3 (STAT3), thus modulating the expression of a broad spectrum of downstream target genes **(van der Zee et al., 2015)**. Numerous studies showed that IL-6 and its downstream effector STAT3 are highly involved in apoptosis, proliferation and survival **(Bellone et al., 2005; Chen et al., 2007) (Figure 1)**.

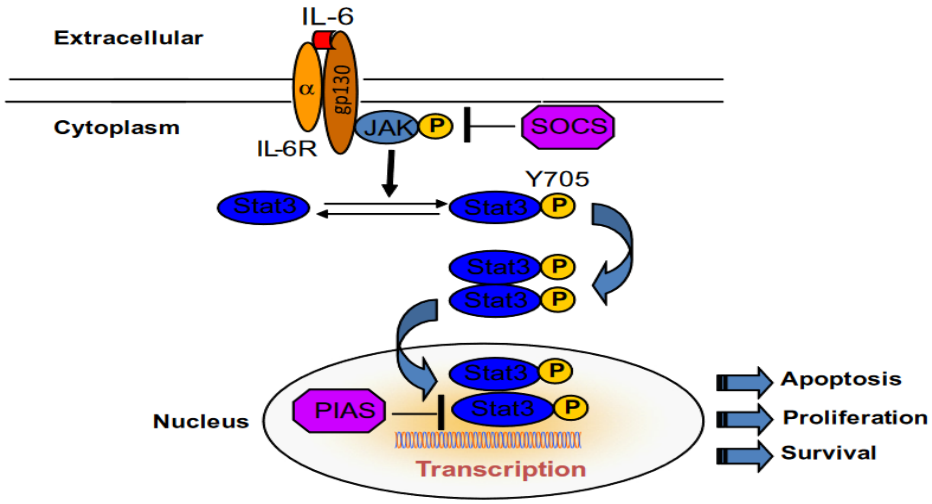

Figure 1: IL-6-Jak-Stat signaling pathway. IL-6 binds to the IL-6Rα and induces a cascade of phosphorylation of JAK kinase that leads to the activation of Stat3. Activated Stat3 translocates to the nucleus where it targets genes involved in apoptosis, proliferation and survival. SOCS and PIAS proteins negatively suppress IL-6-Jak-Stat pathway activity **(Guo et al., 2012).**

4.1.2. Interleukin-6 gene polymorphisms

Five polymorphisms of IL-6 were studied as rs1800796, rs2069837, rs1524107, rs2066992, rs2069840. Among these SNPs, rs1524107, and rs2066992 were identified to have association with EC risk **(Cai et al., 2019)**. Rs1524107 was identified to be associated with several diseases, including rheumatoid arthritis **(Li et al., 2014)**, major depressive disorder **(Zhang et al., 2016)**, Alzheimer's disease **(Chen et al., 2012)**, adult-onset asthma **(Lajunen et al., 2016)**, lung cancer **(Chen et al., 2013)**. For rs2066992, **Juo et al. (2009)** found that there was no significance association of rs2066992 and endometriosis risk. Other studies have found rs206699 to be associated with coronary artery disease **(Ding et al., 2014)**, and chronic hepatitis B virus infection **(Zhao et al., 2013)**.

4.1.3. Interleukin-6 gene polymorphism (rs1800795)

Rs1800795 is a SNP in the promoter of the IL-6 gene, affecting its levels. It is usually referred to as the IL6 "-174" polymorphism in the literature, which is defined as being 174 base pairs (bp) upstream from the transcription start site (-174G>C, rs1800795) **(González-Castro et al., 2019)**.

Rs1800795 tends to be quite polymorphic in Caucasians, but Asian and African populations are almost monomorphic for the (G) allele. Rs1800795 was initially discovered in 1998, when it was found that the rs1800795 (C) allele generates less IL6 than the (G) allele. (CC) genotype of IL-6 rs1800795 polymorphism was suggested to be a protective genotype against systemic onset juvenile rheumatoid arthritis, and in fact, few juvenile RA patients had such genotype **(Fishman et al., 1998)**.

The rs1800795 (G) allele, generally associated with higher levels of IL6, has been associated with increased risk in the studies. The rs1800795 (G) allele was significantly associated with type-2 diabetes (OR=1.51, CI: 1.11-2.07, p=0.0096) in a study of 700 elderly Caucasians **(Illig et al., 2004)**. Following a kidney transplant, patients with rs1800795 (GG) genotypes had a higher risk of new-onset diabetes and higher C-reactive protein levels compared to the (CC) genotype **(Bamoulid et al., 2006)**. In 168 Brazilian patients, rs1800795 (G) allele frequency was higher in gastric cancer than in patients with chronic gastritis **(Gatti et al., 2007)**. A recent study illustrated that that the IL-6 -174G>C polymorphism was associated with ovarian cancer and cervical cancer risk **(Hashemzehi et al., 2021)**.

The association of IL-6 promoter polymorphisms (rs1800795) and EC risk is still unclear. It is well-known that host immune response and chronic inflammation play critical roles in preventing the progression of EC. IL-6, an important pre-inflammatory cytokine, is a multifunctional protein principally involved in the genesis and maintenance of the inflammatory response. Substantially, high levels of IL-6 in the microenvironment may promote tumor angiogenesis and the development of EC. IL-6 was suggested to regulate the anti-apoptotic protein (mcl-1) expression via a PI3K/Akt-dependent pathway that might facilitate the oncogenesis of human EC by modulating the apoptosis threshold. **Wang et al. (2016)** concluded that, the CC genotype of IL-6 gene polymorphisms at positions of −174 might confer a high risk of EC.

4.2. Interleukin-1A

Interleukin-1A (IL-1A) is a member of the interleukin 1 cytokine family and is involved in primarily pro-inflammatory immune processes and hematopoiesis. The IL-1 gene family consists of two major agonistic molecules, namely, IL-1α and IL-1β, and one antagonistic cytokine, the IL-1 receptor antagonist (IL-1Ra). Both IL-1α and IL-1β are produced by lymphocytes or monocytes in the loci of inflammation. Most of the genes coding for the IL-1 family of proteins and clustered on the 2q12-q21 locus (IL-1α, IL-1β, and IL-1Ra) are polymorphic in multiple loci **(Um et al., 2011)**.

Interleukin-1α is produced as a 271-amino acid precursor protein. For transcription of the IL-1α gene, transcription factor specificity protein 1 (Sp1) activates the IL-1α promoter activity in the 5′ - upstream **(Kaneko et al., 2019)**.

Interleukin-1A is constitutively expressed in many cell types in healthy tissues at steady state, and its expression can be increased in response to growth factors and proinflammatory or stress-associated stimuli. Absolute amounts of IL-1α protein vary among cell types, but barrier cells such as endothelial and epithelial cells express substantial amounts of this cytokine at steady state **(Bersudsky et al., 2014)**. The inducible expression of IL-1α depends on the presence of binding sites for activator protein 1 (AP1) and Nuclear factor kappa-B (NF-κB) transcription factors **(Di Paolo and Shayakhmetov, 2016)**, which can upregulate

IL-1α expression in a cell-type-specific manner.

Monocytes have a unique mechanism of inducible IL-1A expression that involves upregulation of the long noncoding RNA, a natural antisense transcript that is partially complementary to IL-1α mRNA **(Chan et al., 2015)**. Although constitutive IL-1α expression is likely to be regulated by Sp1-family transcription factors in terminally differentiated cells, inducible IL-1α expression occurs rapidly in response to a variety of physiological stimuli, including oxidative stress, lipid overload, hormonal stimulation, and exposure to cytokines (including IL-1β and IL-1α itself). The responsiveness of the IL-1A promoter to such a broad spectrum of stimuli, which trigger inducible expression of IL-1α in addition to its constitutive expression in both hematopoietic and nonhematopoietic cells, has important implications for IL-1α's ability to drive sterile and pathogen-induced inflammation **(Di Paolo and Shayakhmetov, 2016)**.

The expression patterns of IL-1 vary; it is expressed in an autocrine or paracrine fashion. IL-1 exhibits autocrine behavior by stimulating the tumor cell itself to invade and proliferate, or it can exert paracrine effects on stromal cells in the microenvironment. The exact mechanisms by which IL-1 promotes tumor growth remain unclear, though the protein is believed to act primarily indirectly **(Lewis et al., 2006) (Figure 2)**.

4.2.1. Interleukin-1A in endometrial carcinoma

Previous studies have demonstrated that IL-1A is significantly related to the risk of endometrial, prostate, lung, colon, cervical, and breast cancer, etc. **(Song et al., 2016; Malik and Kanneganti, 2018)**. Aging cells produce IL-1A and other proinflammatory mediators that sustain the low-grade chronic inflammation underlying many age-related pathologies and cancer. Normal human fibroblasts have an increase in NF-κB activity, which stimulates production of proinflammatory mediators such as IL-6 and IL-8. This NF-κB activity is due to an increase in IL-1α translation, leading to production of membrane-bound IL-1α that stimulates cells in an autocrine manner **(Di Paolo and Shayakhmetov, 2016)**.

4.2.2. Interleukin-1A gene polymorphisms

Interleukin-1A, which encodes IL-1α protein, locates at chromosome 2q and consists of 7 exons and 6 introns. Rs17561, rs1800587, and rs3783553 are three SNPs on IL1A gene, which are believed to have functional roles. Rs17561 is a mutation at +4845 of 5th exon of IL1A, which leads to the G-to-T variation, as well as the change of amino acid. Rs1800587(C-to-T) located at -889 of IL1A promoter region, may affect the expression of IL-1α. In addition, rs3783553 SNP occurrs within the IL1A 3'-untranslated regions (UTR) and may affects the expression of IL-1α by influencing the binding of miR-122. That's an insertion/deletion variation **(Um et al., 2011)**.

Results of a genetic case-control study by **Hata et al. (2013)** demonstrated that four common SNPs of IL1A, rs3783553, rs2856836, rs1304037, and rs17561, were significantly associated with susceptibility to endometriosis in Japanese population **(Hata et al., 2013)**.

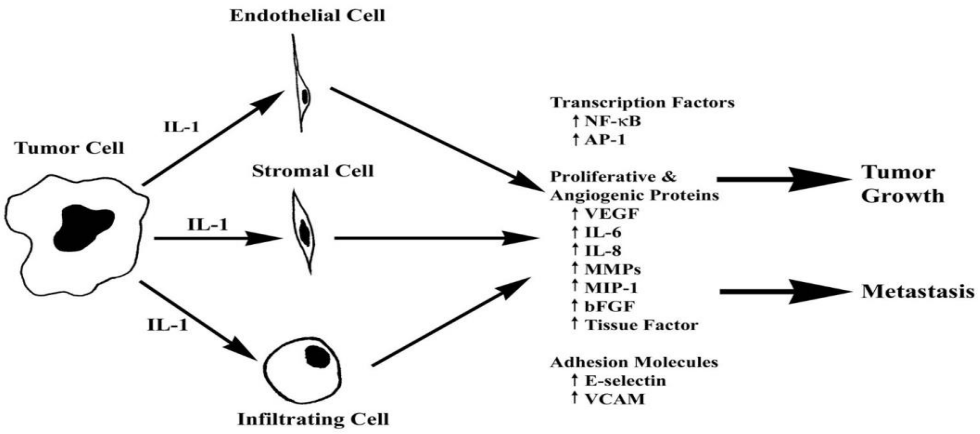

Figure 2: Proposed model of how IL-1 indirectly alters tumor growth and metastatic potential in vivo. In the tumor micro-environment, IL-1 has local effects on host infiltrating cells that result in production of proangiogenic and prometastatic mediators **(Lewis et al., 2006)**.

4.2.3. Interleukin-1A gene polymorphism (rs1800587)

The IL-1A gene is localized on the long arm of chromosome 2 (2q14), harbors a common polymorphism (rs1800587) on the 5′ -regulatory region: C to T transition at position −889, which is within a transcriptional regulatory region **(Wang and Wang, 2021)**. Previous researches have shown that the TT genotype was reported to increase promoter activity, producing increased levels of IL-1A mRNA and IL-1A, compared with those of CC genotype **(Huynh-Ba et al., 2007)**. Several meta-analyses have reported an association between rs1800587 polymorphism and the presence of various autoimmune diseases, including systemic lupus erythematosus, multiple sclerosis, and Graves' disease **(Huang et al., 2013; Song et al., 2014)**. The role of IL-1A (rs 1800587) genetic polymorphism was found in the pathogenesis of uterine hyperplastic processes **(Altuchova et al., 2014)**. According to literature data, this genetic variant significantly increases the level of IL-1α. Reportedly, increasing of this cytokine's level is associated with activation of endothelial cells with increasing expression of adhesive molecules, activation of neutrophiles and increased synthesis of acute-phase proteins. Besides, IL-1 has stimulatory effect on T- and B-lymphocytes; it is able to activate synthesis of other cytokines (IL-2, -3, -4, -5, -6, -7, -8) **(Favorov et al., 2005)**.

5. Conclusion

Endometrial carcinoma is one of most the common gynecologic malignancy. Recent studies have concentrated on developing new potential biomarkers that will exhibit enough sensitivity and specificity in EC clinical practise. Endometrial carcinoma and cytokines are linked in an alarming way, providing a substantial public health risk. Interleukin 6 and Interleukin 1A and their polymorphisms serve as diagnostic and prognostic markers which they can predict the development of EC. This review outlines the findings of the relationship between classic and novel cytokines and EC risk.

6. Conflict of interest

None of the authors have any conflicts of interest.

References

Aksel, T. Z. and A. T. Çakir. Tumor Markers in Endometrial Cancer. Curr Obstet Gynecol Rep. 2020: 9 (1): 15-20.

Alshahrani, S., A. S. Soliman, A. Hablas, M. Ramadan, J. L. Meza, S. Remmenga, I. A. Seifeldein and R. M. Chamberlain, 2018. Changes in Uterine Cancer Incidence Rates in Egypt. Obstet Gynecol Int, 2018, 3632067.

Altuchova, O., N. Demakova, O. Koneva, S. P. Pachomov, V. S. Orlova, and O.V. Golovchenko, 2014. Genetic factors of uterine hyperplastic processes. Res J Pharm Biol Chem Sci, 6 (5): 1397-1400.

American Cancer Society. Key statistics for endometrial cancer, 2020. Available at: https://www.cancer.org/cancer/endometrial-cancer/about/key-statistics.html.

Angioli, R., S. Capriglione, G. Scaletta, A. Aloisi, A. Miranda, C. De Cicco Nardone, C. Terranova and F. Plotti, 2016. The role of HE4 in endometrial cancer recurrence: how to choose the optimal follow-up program. Tumour Biol, 37(4), 4973-4978.

Bamoulid, J., C. Courivaud, M. Deschamps, P. Mercier, C. Ferrand, A. Penfornis, P. Tiberghien, J. M. Chalopin, P. Saas and D. Ducloux, 2006. IL-6 promoter polymorphism -174 is associated with new-onset diabetes after transplantation. J Am Soc Nephrol, 17(8), 2333-2340.

Bellone, S, K. Watts, S. Cane, M. Palmieri, M. J. Cannon, A. Burnett, J. J. Roman, S. Pecorelli and A. D. Santin, 2005. High serum levels of interleukin-6 in endometrial carcinoma are associated with uterine serous papillary histology, a highly aggressive and chemotherapy-resistant variant of endometrial cancer. Gynecol Oncol, 98(1):92-98.

Bersudsky, M., L. Luski, D. Fishman, R. M. White, N. Ziv-Sokolovskaya, S. Dotan, P. Rider, I. Kaplanov, T. Aychek, C. A. Dinarello, R. N. Apte and E. Voronov, 2014. Non-redundant properties of IL-1α and IL-1β during acute colon inflammation in mice. Gut, 4 (63), 598-609.

Bian, J., X. Sun, B. Li and L. Ming, 2017. Clinical Significance of Serum HE4, CA125, CA724, and

CA19-9 in Patients Wwith Endometrial Cancer. Technol Cancer Res Treat. 16(4), 435-439.

Bray, F., J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A., Torre and A. Jemal, 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 68-394.

Brüggmann, D., K. Ouassou, D. Klingelhöfer, M. K. Bohlmann, J. Jaque and D. A. Groneberg, 2020. Endometrial cancer: mapping the global landscape of research. J Transl Med, 18(1), 386.

Burke, W. M., J. Orr, M. Leitao, E. Salom, P. Gehrig, A. B. Olawaiye, M. Brewer, D. Boruta, T. J. Herzog and F. A. Shahin, 2014. Endometrial cancer: a review and current management strategies: part II. Gynecol Oncol, 134(2), 393-402.

Cabia B., S. Andrade, M. C. Carreira, F. F. Casanueva and A. B. Crujeiras, 2016. A role for novel adipose tissue-secreted factors in obesity-related carcinogenesis. Obes Rev, 17(4), 361-376.

Cai, J., K. Cui, F. Niu, T. Jin, S. Huang, Y. Zhang, and S. Bao, 2019. Genetics of IL6 polymorphisms: Case-control study of the risk of endometrial cancer. Mol Genet Genomic Med, 7(4), e00600.

Cai, S., Y. X. Zhang, K. Han and Y. Q. Ding, 2017. Expressions and clinical significance of COX-2, VEGF-C, and EFGR in endometrial carcinoma. Arch Gynecol Obstet, 296 (1), 93-98.

Chan, J., M. Atianand, Z. Jiang, S. Carpenter, D. Aiello, R. Elling, K. A. Fitzgerald and D. R. Caffrey, 2015. Cutting Edge: A Natural Antisense Transcript, AS-IL1α, Controls Inducible Transcription of the Proinflammatory Cytokine IL-1α. J Immunol, 4 (195), 1359-1363.

Che, Q., B. Y. Liu, Y. Liao, H. J. Zhang, T. T. Yang, Y. Y. He, Y. H. Xia, W. Lu, X. Y. He, Z. Chen, F. Y. Wang and X. P. Wan, 2014. Activation of a positive feedback loop involving IL-6 and aromatase promotes intratumoral 17β-estradiol biosynthesis in endometrial carcinoma microenvironment. Int J Cancer, 135(2), 282-294.

Chen, C. L., F. C. Hsieh, J. C. Lieblein, J. Brown, C. Chan, J. A. Wallace, G. Cheng, B. M. Hall and J. Lin, 2007. Stat3 activation in human endometrial and cervical cancers. Br J Cancer, 96 (4), 591-599.

Chen, J., R. Y. Liu, L. Yang, J. Zhao, X. Zhao, D. Lu, N. Yi, B. Han, X. F. Chen, K. Zhang, J. He, Z. Lei, Y. Zhou, B. Pasche, X. Li and H. T. Zhang, 2013. A two-SNP IL-6 promoter haplotype is associated with increased lung cancer risk. J Cancer Res Clin Oncol, 139(2), 231-242.

Chen, S.Y., T. F. Chen, L. C. Lai, J. H. Chen, Y. Sun, L. L. Wen, P. K. Yip, Y. M. Chu and Y. C. Chen, 2012. Sequence variants of interleukin 6 (IL-6) are significantly associated with a decreased risk of late-onset Alzheimer's disease. J Neuroinflammation, 9, 21.

Cheng, D., Y. Sun and H. He, 2014. Diagnostic role of circulating YKL-40 in endometrial carcinoma patients: a meta-analysis of seven related studies. Med Oncol, 31(12), 326.

Cocco, E., S. Bellone, K. El-Sahwi, M. Cargnelutti, F. Casagrande, N. Buza, F. A. Tavassoli, E. R. Siegel, I. Visintin, E. Ratner, D. A. Silasi, M. Azodi, P. E. Schwartz, T. J. Rutherford, S. Pecorelli and A. D. Santin, 2009. Serum amyloid A (SAA): a novel biomarker for uterine serous papillary cancer. Br J Cancer, 101(2), 335-341.

Cocco, E., S. Bellone, K. El-Sahwi, M. Cargnelutti, N. Buza, F. A. Tavassoli, P. E. Schwartz, T. J. Rutherford, S. Pecorelli and A. D. Santin, 2010. Serum amyloid A: a novel biomarker for endometrial cancer. Cancer, 116 (4), 843-851.

Cuesta-Guardiola, T., A. Q. Carretero, J. Martinez-Martinez, Y. Cuñarro-López, A. Pereira-Sánchez, A. Fernández-Corona and J. A. de Leon-Luis, 2021. Identification and characterization of endometrial carcinoma with tumor markers HE4 and CA125 in serum and endometrial tissue samples. J Turk Ger Gynecol Assoc, 22(3), 161-7.

Cymbaluk-Płoska, A, A. Chudecka-Głaz, E. Pius-Sadowska, B. Machaliński, A. Sompolska-Rzechuła, S. Kwiatkowski and J. Menkiszak, 2019. The role of lipocalin-2 serum levels in the diagnostics of endometrial cancer. Cancer Biomark, 24 (3), 315-324.

Cymbaluk-Płoska, A., A. Chudecka-Głaz, E. Pius-Sadowska, A. Sompolska-Rzechuła, K. Chudecka, M. Bulsa, B. Machaliński and J. Menkiszak, 2017. Clinical Relevance of NGAL/MMP-9 Pathway in Patients with Endometrial Cancer. Dis Markers, 2017, 6589262.

Di Paolo, N.C. and D. M. Shayakhmetov, 2016. Interleukin 1α and the inflammatory process. Nat Immunol, 17(8), 906-913.

Ding, Y., D. Yang, X. Xun, Z. Wang, P. Sun, D. Xu, P. He, H. Niu and T. Jin, 2014. Association of genetic polymorphisms with chronic obstructive pulmonary disease in the Hainan population: a case-control study. Int J Chron Obstruct Pulmon Dis, 10, 7-13.

Drygin, D., C. B. Ho, M. Omori, J. Bliesath, C. Proffitt, R. Rice, A. Siddiqui-Jain, S. O'Brien, C. Padgett, J. K. Lim, K. Anderes, W. G. Rice and D. Ryckman, 2011. Protein kinase CK2 modulates IL-6 expression in inflammatory breast cancer. Biochem Biophys Res Commun, 415(1), 163-167.

Fan J. T., X. H. Si, Y. Liao and P. Shen, 2013. The diagnostic and prognostic value of serum YKL-40 in endometrial cancer. Arch Gynecol Obstet, 287(1), 111-115.

Favorov, A. V., T. V. Andreewski, M. A. Sudomoina, O. O. Favorova, G. Parmigiani and M. F. Ochs, 2005. A Markov chain Monte Carlo technique for identification of combinations of allelic variants underlying complex diseases in humans. Genetics, 4 (171), 2113-2121.

Fishman, D., G. Faulds, R. Jeffery, V. Mohamed-Ali, J. S. Yudkin, S. Humphries and P. Woo, 1998. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J Clin Invest, 102 (7), 1369-1376.

Gatti, L. L., R. R. Burbano, M. Zambaldi-Tunes, R. W. de-Lábio, P. P. de Assumpção, M. de Arruda Cardoso-Smith and S. L. Marques-Payão, 2007. Interleukin-6 polymorphisms, Helicobacter pylori infection in adult Brazilian patients with chronic gastritis and gastric adenocarcinoma. Arch Med Res, 38(5), 551-555.

GLOBOCAN Egypt fact sheet for cancer, 2020. Last assessed on July 2022. Available at: https:// gco.iarc.fr/today/data/factsheets/populations/818-egypt-fact-sheets.pdf.

González-Castro, T.B., Y. Hernández-Díaz, N. Pérez-Hernández, C. A. Tovilla-Zárate, I. E. Juárez-Rojop, M. L. López-Narvaez, R. Blachman-Braun, R. Posadas-Sánchez, G. Vargas-Alarcón, E. García-Flores, B. G. Cazarín-Santos, V. M. Borgonio-Cuadra, P. A. Reyes-López, J. M. Rodríguez-Pérez, 2019. Interleukin 6 (rs1800795) gene polymorphism is associated with cardiovascular diseases: a meta-analysis of 74 studies with 86,229 subjects. EXCLI J, 18, 331-355.

Guo, Y., F. Xu, T. Lu, Z. Duan and Z. Zhang, 2012. Interleukin-6 signaling pathway in targeted therapy for cancer. Cancer Treat Rev, 38 (7), 904-910.

Hashemzehi, A., M. Karimi-Zarchi, S. F. Parsaeian, F. Asadian, H. Golestanpour, S. Setayesh, S. A. Shaker, M. Zare-Shehneh and H. Neamatzadeh, 2021. Association of IL-6 -174G>C and -572G>C Polymorphisms with Susceptibility to Cervical Cancer and Ovarian Cancer. Asian Pac J Cancer Prev, 22(9), 2867-2871.

Hata, Y., H. Nakaoka, K. Yoshihara, S. Adachi, K. Haino, M. Yamaguchi, N. Nishikawa, K. Kashima, T. Yahata, A. Tajima, A. Watanabe, S. Akira, K. Hosomichi, I. Inoue, K. Tanaka, 2013. A nonsynonymous variant of IL1A is associated with endometriosis in Japanese population. J Hum Genet, 58(8), 517-520.

He, Y., J. Wang, C. X. Ma and Y. H. Kangm, 2020. Role of Human Epididymis Protein 4 (HE4) in Determining Survival of Patients with Endometrial Cancer: A Meta-Analysis. Technol Cancer Res Treat, 19, 1533033820971660.

Hirano, T, 2021. IL-6 in inflammation, autoimmunity and cancer. Int Immunol, 33 (3), 127-148.

Huang, J., Z. K. Xie, R. B. Lu and Z. F. Xie, 2013. Association of interleukin-1 gene polymorphisms with multiple sclerosis: a meta-analysis. Inflamm Res, 62(1), 97-106.

Huynh-Ba, G., N. P. Lang, M. S. Tonetti and G. E. Salvi, 2007. The association of the composite IL-1 genotype with periodontitis progression and/or treatment outcomes: A systematic review. J Clin Periodontol, 4 (34), 305-317.

Illig, T., F. Bongardt, A. Schöpfer, S. Müller-Scholze, W. Rathmann, W. Koenig, B. Thorand, C. Vollmert, R. Holle, H. Kolb and C. Herder, 2004. Kooperative Gesundheitsforschung im Raum Augsburg/Cooperative Research in the Region of Augsburg. Significant association of the interleukin-6 gene polymorphisms C-174G and A-598G with type 2 diabetes. J Clin Endocrinol Metab, 89(10), 5053-5058.

Jemal, A. F. Bray, M. M. Center, J. Ferlay, E. Ward and D. Forman, 2011. Global cancer statistics. CA Cancer J Clin, 61, 69–90.

Juo S.H., R. Wu, C. S. Lin, M. T. Wu, J. N. Lee and E. M. Tsai, 2009. A functional promoter polymorphism in interleukin-10 gene influences susceptibility to endometriosis. Fertil Steril, 92(4), 1228-1233.

Kaneko, N., N. Kaneko, M. Kurata, T. Yamamoto, S. Morikawa, J. Masumoto, 2019. The role of interleukin-1 in general pathology. Inflamm Regen, 6, 39, 12.

Kemik, P., B. Saatli, N. Yıldırım, V. D. Kemik, B. Deveci, M. C. Terek, S. Koçtürk, M. Koyuncuoğlu, U. Saygılı, 2016. Diagnostic and prognostic values of preoperative serum levels of YKL-40, HE-4 and DKK-3 in endometrial cancer. Gynecol Oncol, 140 (1), 64-69.

Kotowicz, B., M. Fuksiewicz, J. Jonska-Gmyrek, M. Wagrodzki and M. Kowalska, 2017. Preoperative serum levels of YKL 40 and CA125 as a prognostic indicators in patients with endometrial cancer. Eur J Obstet Gynecol Reprod Biol, 215, 141-147.

Lajunen, T. K., J. J. Jaakkola and M. S. Jaakkola, 2016. Interleukin 6 SNP rs1800797 associates with the risk of adult-onset asthma. Genes Immun, 17 (3), 193-198.

Lewis, A. M., S. Varghese, H. Xu and H. R. Alexander, 2006. Interleukin-1 and cancer progression: the emerging role of interleukin-1 receptor antagonist as a novel therapeutic agent in cancer treatment. J Transl Med, 4, 48.

Li, F., J. Xu, J. Zheng, J. Sokolove, K. Zhu, Y. Zhang, H. Sun, E. Evangelou and Z. Pan, 2014. Association between interleukin-6 gene polymorphisms and rheumatoid arthritis in Chinese Han population: a case-control study and a meta-analysis. Sci Rep, 4, 5714.

Li, Y., P. Cong, P. Wang, C. Peng, M. Liu and G. Sun, 2019. Risk factors for pelvic lymph node metastasis in endometrial cancer. Arch Gynecol Obstet. 300(4), 1007-1013.

Lin, H. Y., G. Q. Tan, Y. Liu and S. Q. Lin, 2019. The prognostic value of serum amyloid A in solid tumors: a meta-analysis. Cancer Cell Int, 19, 62.

Mahecha, A. M. and H. Wang, 2017. The influence of vascular endothelial growth factor-A and matrix metalloproteinase-2 and -9 in angiogenesis, metastasis, and prognosis of endometrial cancer. Onco Targets Ther, 10, 4617-4624.

Malik, A. and T. D. Kanneganti, 2018. Function and regulation of IL-1α in inflammatory diseases and cancer. Immunol Rev, 281 (1), 124-137.

Masjedi, A., V. Hashemi, M. Hojjat-Farsangi, G. Ghalamfarsa, G. Azizi, M. Yousefi and F. Jadidi-Niaragh, 2018. The significant role of interleukin-6 and its signaling pathway in the immunopathogenesis and treatment of breast cancer. Biomed Pharmacother, 108, 1415-1424.

Mohammad, H. F., N. El-Khazragy, S. Hassan, F. Abukra, R. M. Abdelrahman, A. A. Riad and M. A. Abdelhafee, 2022. HE4 is a Beneficial Biomarker in Endometrial Adenocarcinoma. Current Women's Health Reviews, 18(2), 141-148.

Morice, P., A. Leary, C. Creutzberg, N. Abu-Rustum and E. Darai, 2016. Endometrial cancer. Lancet, 387(10023), 1094-1108.

Nithin, K. U., M. G. Sridhar, K. Srilatha and S. Habebullah, 2018. CA 125 is a better marker to differentiate endometrial cancer and abnormal uterine bleeding. Afr Health Sci, 18(4), 972-978.

Omer, B., S. Genc, O. Takmaz, A. Dirican, Z. Kusku-Kiraz, S. Berkman and F. Gurdol, 2013. The diagnostic role of human epididymis protein 4 and serum amyloid-A in early-stage endometrial cancer patients. Tumour Biol, 34 (5), 2645-2650.

Passarello. K., S. Kurian and V. Villanueva, 2019. Endometrial Cancer: An Overview of Pathophysiology, Management, and Care. Semin Oncol Nurs, 35 (2), 157-165.

Song, G. G., J. H. Kim, Y. H. Seo, S. J. Choi, J. D. Ji and Y. H. Lee, 2014. Associations between interleukin 1 polymorphisms and susceptibility to systemic lupus erythematosus: a meta-analysis. Hum Immunol, 75(1), 105-112.

Song, Z., Y. Lin, X. Ye, C. Feng, Y. Lu, G. Yang and C. Dong, 2016. Expression of IL-1α and IL-6 is Associated with Progression and Prognosis of Human Cervical Cancer. Med Sci Monit, 22, 4475-4481.

Soufla, G., S. Sifakis, F. Porichis and D. A. Spandidos, 2013. Prognostic value of tgfb1 protein in endometrioid adenocarcinoma. Eur J Clin Invest, 43(1), 79-90.

Torre, L. A., F. Bray, R. L. Siegel, J. Ferlay, J. Lortet-Tieulent and A. Jemal, 2015. DFT-

comparison of anti-cancer effect of ibuprofen drug anions and breast cancer treatment by ethanolic solution of nitrobenzaldehyde in two hours. CA A Cancer J Clin, 65, 87–108.

Ueda, Y., T. Enomoto, T. Kimura, T. Miyatake, K. Yoshino, M. Fujita and T. Kimura, 2010. Serum biomarkers for early detection of gynecologic cancers. Cancers (Basel), 2(2), 1312-1327.

Um, J.Y., H. K. Rim, S. J. Kim, H. L. Kim and S. H. Hong, 2011. Functional polymorphism of IL-1 alpha and its potential role in obesity in humans and mice. PLoS One, 6(12), e29524.

Vălu, V., and O. TOMA, 2017. ENDOMETRIAL CANCER. A REVIEW AND EVALUATION OF RISK FACTORS. Analele ştiinţifice ale Universităţii "Al. I. Cuza" din Iaşi. Secţiunea IIIc, Ştiinţe economice (1976), XVIII(3).

van der Zee, M., A. Sacchetti, M. Cansoy, R. Joosten, M. Teeuwssen, C. Heijmans-Antonissen, P. C. Ewing-Graham, C. W. Burger, L. J. Blok and R. Fodde, 2015. IL6/JAK1/STAT3 Signaling Blockade in Endometrial Cancer Affects the ALDHhi/CD126+ Stem-like Component and Reduces Tumor Burden. Cancer Res, 75(17), 3608-3622.

Wang, C., D. A. Tran, M. Z. Fu, W. Chen, S. W. Fu and X. Li, 2020. Estrogen Receptor, Progesterone Receptor, and HER2 Receptor Markers in Endometrial Cancer. J Cancer. 16, 11(7):1693-1701.

Wang, H. and Y. Wang, 2021. Association between interleukin-1 alpha rs1800587 polymorphism and rheumatoid arthritis: A meta-analysis. Sci Prog, 2 (104), 00368504211013647.

Wang, H. Y., J. J. Zhang, X. Y. Zheng, J. H. Liu and Y. W. Li, 2016. Association between IL-6 Gene (-174 & -572 G/C) Polymorphisms and Endometrial Adenocarcinoma Risk. Pathol Oncol Res, 22 (4), 825-829.

Xu, H. X. Sun and W. J. Sun, 2018. Expression and clinical correlation of NGAL and VEGF in endometrial carcinoma. Eur Rev Med Pharmacol Sci, 22(3), 632-636.

Yang, Y., J. Xiao, L. Tang, B. Wang, X. Sun, Z. Xu, L. Liu and S. Shi, 2022. Effects of IL-6 Polymorphisms on Individual Susceptibility to Allergic Diseases: A Systematic Review and Meta-Analysis. Front Genet, 13, 822091.

Yu D. S., C. L. Wu, S. Y. Ping, Y. L. Huang and K. H. Shen, 2014. NGAL can alternately mediate sunitinib resistance in renal cell carcinoma. J Urol, 192(2), 559-566.

Zeng, X., J. Li, L. N. Kang, M. R. Xi and G. D. Liao, 2020. Potential clinical value of interleukin-31 and interleukin-33 with their receptors expression as diagnostic and predictive factors in endometrial cancer: a case-control study. Int J Clin Exp Pathol, 13(6), 1324-32.

Zhang, C., Z. Wu, G. Zhao, F. Wang and Y. Fang, 2016. Identification of IL6 as a susceptibility gene for major depressive disorder. Sci Rep, 9, 6, 31264.

Zhao, X. M., Y. F. Gao, Q. Zhou, F. M. Pan and X. Li, 2013. Relationship between interleukin-6 polymorphism and susceptibility to chronic hepatitis B virus infection. World J Gastroenterol, 19(40), 6888-6893.