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A review of Molecular Mechanism of Endometrial Carcinoma Invasion and Tumor Markers

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ABSTRACT

The tumorigenesis of endometrial carcinoma (EC) is a complicated process involving numerous dysregulated genes. Moreover, EC can be caused by genetic disorders, and serum levels of various tumor markers are increased in 20% to 30% of EC patients. EC patients' survival is significantly associated with several accepted prognostic factors such as stage, grade and histotype of the disease established by Buchman classification, and FIGO (International Federation of Gynecology and Obstetrics). Recent developments in molecular research have revealed the landscape of genetic abnormalities found in EC and have shed light on the disease's pathogenesis to allow the earlier detection of EC. In this review, we discuss the development of diagnostic tools for the early detection of EC to improve outcomes for patients. Furthermore, we describe the current molecular mechanism of it.

Keywords: endometrial carcinoma, FIGO, tumor markers, molecular mechanism.

1. Epidemiology

Endometrial carcinoma (EC) is an increasingly problematic gynecological cancer **(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).** Moreover, EC was the second most common and the fourth leading cause of death due to gynecological cancer among women worldwide in 2018 **(Bray et al., 2018)**.

According to the International Agency for Research on Cancer, the incidence rate of EC is increasing rapidly compared with 2018, and is estimated to increase by more than 50% worldwide by 2040 **(Zhang et al., 2019)**. Endometrial carcinoma is the most common gynecological cancer in high-income countries and the sixth most prevalent diagnosed cancer in females worldwide **(Wang et al., 2020).** Egypt and South Africa have the highest rates of EC in Africa (**Brüggmann et al., 2020)**. Based on Globocan, corpus uteri cancer is ranked as the tenth most common cancer among women in Egypt. According to the Middle East Cancer Consortium (MECC) Report, the incidence rate of uterine cancer in Egypt (3.5/100,000) is the lowest compared to other countries in the Middle East. In addition, the low stage at diagnosis of uterine cancer is high compared to other female cancers in Egypt **(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 attributes and characteristics that increase the likelihood of developing a disease. In the case of EC, the most significant risk factors are age, race, metabolic syndrome, unopposed estrogen exposure, and genetic predispositions to EC **(American Cancer Society, 2022)**.

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 85 percent of cases occurring after the age of 50 and only 5 percent occurring before the age of 40. Young premenopausal women diagnosed with EC have a higher BMI, anovulatory cycles, and/or a genetic predisposition to develop EC **(Passarello et al., 2019)**.

2.2. Race

The race of a woman appears to be important in the development of EC, with rates highest in North America, Northern Europe, Asia and Africa and lowest in Eastern Europe and Latin America. Obesity prevalence, metabolic syndrome, and hormone replacement therapy, as well as general population ageing, may all contribute to these rates **(Burke et al., 2014)**.

2.3. Metabolic Syndrome

Metabolic syndrome is a gathering of risk factors linked to an increased risk of diabetes, stroke, heart disease, and other serious health problems. Elevated blood pressure, elevated triglycerides, decreased high-density lipoprotein (HDL) cholesterol, central obesity, and high blood glucose are all risk factors for metabolic syndrome **(Burke et al., 2014)**.

2.4. Unopposed Estrogen Exposure

Prolonged estrogen exposure without progestin resistance is a risk factor for type I EC. Estrogen exposure can occur in both exogenous and endogenous 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)**.

Risk factors associated with estrogen excess:

A) Obesity:

Obesity is the most prominent risk factor for hyperplasia evolving into malignant carcinoma of the endometrium **(Nees et al., 2022)**.

B) Hormone replacement therapy:

Exogenous estrogen exposure occurs when estrogen is replaced with medication to control menopausal symptoms. Unopposed estrogen replacement can increase the risk of developing EC by up to 20 times, with the length of use increasing the risk. This risk is significantly reduced when progestins are used concurrently **(Tempfer et al., 2020).**

C) Reproductive factors:

Tamoxifen therapy has also been linked to an increased risk of developing EC and early menarche. Tamoxifen, an estrogen antagonist in breast tissues but an agonist in bone and endometrial tissues, is a selective estrogen receptor modulator. Most studies have discovered that women taking tamoxifen have a two- to three-fold higher relative risk of developing EC than the general population **(Ignatov and Ortmann, 2020)**.

2.5. Genetic Predisposition

Sporadic mutations are responsible for the majority of ECs; The tumorigenesis of EC is a complicated process involving numerous dysregulated genes **(Fatima et al., 2021),** and caused by many genetic disorders **(Yang et al., 2020).** ECs caused by genetic predispositions typically occur 10 to 20 years before sporadic EC **(Passarello et al., 2019)** and are discussed below:

A) Lynch syndrome (LS; hereditary nonpolyposis colorectal cancer):

One of four DNA mismatch repair genes in the germline is mutated in the autosomal dominant syndrome known as LS (MLH1, MSH2, MSH6, or PMS2). It is linked to a significantly higher lifetime risk of colorectal and ECs, as well as a higher risk of biliary tract, brain, small intestine, gastric, ovarian, pancreatic, ureter, and renal cancers **(Gupta et al., 2017; Koh et al., 2018)**.

B) Cowden syndrome:

Cowden syndrome is an autosomal dominant syndrome characterized by phosphatase and tensin homolog (PTEN) mutations **(Mester and Eng, 2015)**. It is associated with a 19% to 28% risk of EC by age 70 **(Staff et al., 2016)**.

3. Endometrial Carcinoma Precursors

3.1. Atypical Endometrial Hyperplasia

Atypical Endometrial hyperplasia (AEH) is a condition of excessive proliferation of the cells of the endometrium, or inner lining of the uterus and thought to be a precursor to EC. The risk of progression to carcinoma was 1% for simple hyperplasia, 3% for complex hyperplasia, 8% for simple AEH, and 29% for complex AEH **(Cybulska and Leitao, 2019)**.

3.2. Endometrial Intraepithelial Neoplasia

Endometrial intraepithelial neoplasia (EIN) is a premalignant lesion of the uterine lining that predisposes to endometrioid endometrial adenocarcinoma. It is composed of a collection of abnormal endometrial cells, arising from the glands that line the uterus, which have a tendency over time to progress to the most common form of uterine cancer—endometrial adenocarcinoma, endometrioid type. EIN has been shown to better predict underlying carcinoma and may be a true precursor entity. Theoretically, all EIN cases would be AEH, but not all AEH cases would be EIN. In practice, strict application of EIN criteria can lead to the classification of disordered proliferative endometrium, a physiologic variant of normal in the perimenopausal state, and benign papillary change as EIN **(Cybulska and Leitao, 2019)**.

4. Clinical-pathological parameters of EC

4.1. Endometrial Carcinoma Staging

The EC is currently staged using International Federation of Gynecology and Obstetrics (FIGO) system and Buchman classification **(Wang et al., 2020; Luna et al., 2021) (Figure 1).**

2.4.2. Endometrial Carcinoma Grading

The ECs are classified as grade 1–3 using FIGO grading system, which is based on the proportion of non-squamous solid growth **(Table 1) (Figure 2) (Mills, 2019).** The Gynecologic Oncology Group (GOG) released an updated clause to the system that allows for a one-step upgrade (e.g., grade 1 → 2, grade 2 → 3) on the basis of severe cytologic atypia irrespective of the percentage of solid growth. The FIGO grading system also applies to mucinous ECs as they are considered close relatives of endometrioid carcinomas **(Winham et al., 2014)**. The system proposed in 2005 combines papillary/solid growth, mitotic activity and nuclear atypia to divide endometrioid tumors into low-grade and high-grade (**Alkushi et al., 2005**).

2.4.3. Endometrial Carcinoma histological type

The vast majority of ECs are adenocarcinomas of two main types. Although there is overlap between the categories, they may be distinguished by using immunohistochemistry of the EC tissue **(Figure 3)**.

Type I (endometrioid adenocarcinoma): happened on peri- and postmenopausal, low parity, high socio-economic status, obesity, diabetes, hypertension, hyperoestrogenism (hormonal therapy, endogenous or secreting tumour, e.g., ovarian sex cord-stromal), Estrogen receptor (ER) positive, background endometrial hyperplasia, microsatellite instability/PTEN mutations.

Type II [(serous and clear cell adenocarcinomas, (carcinosarcoma)]: happened on older patients, more aggressive, atrophic endometrium with precursor serous endometrial intraepithelial carcinoma (EIC), overproduction of ER and p53 mutation **(Shah and Ervine, 2020).**

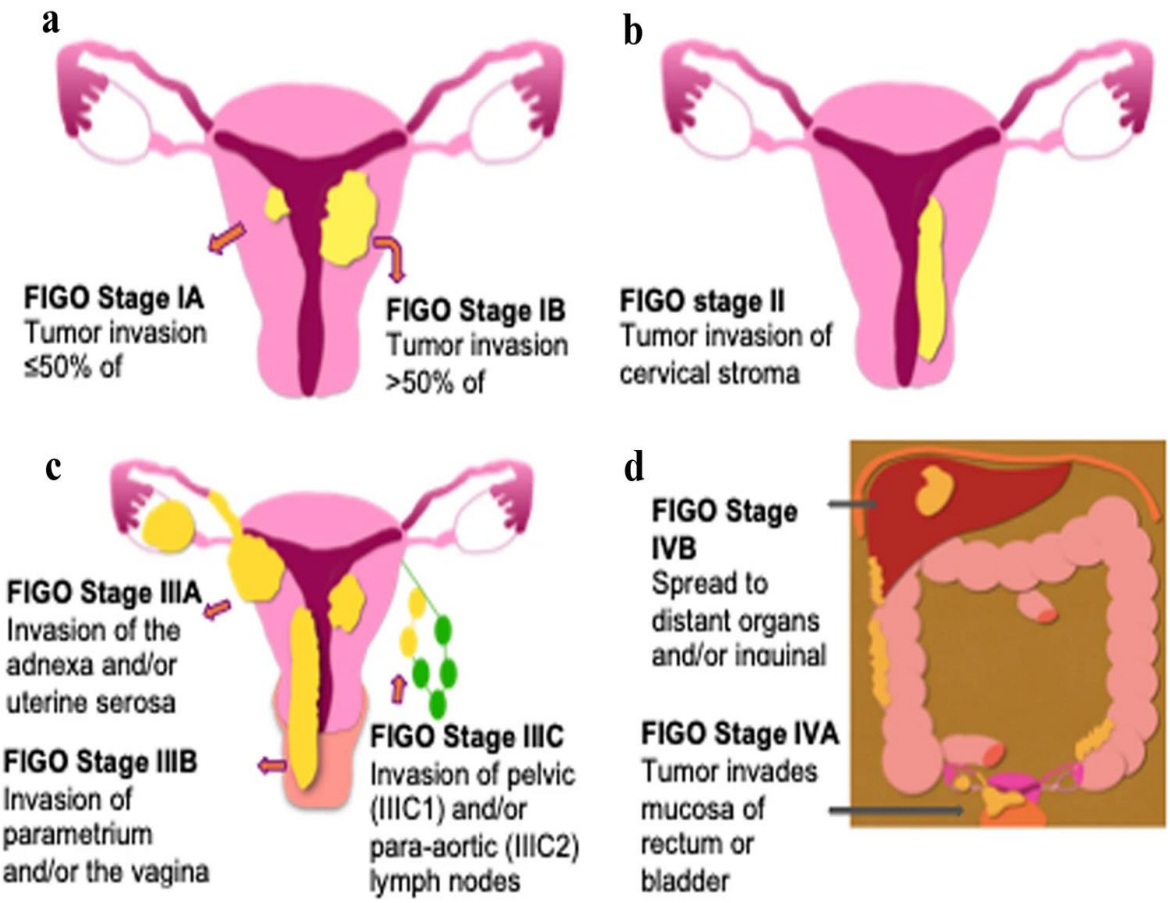

Figure (1): Illustrated FIGO staging system for endometrial cancer. **(a)** Stage 1 disease is subdivided according to depth of myometrial invasion. **(b)** Stage II disease is confined to the uterus. **(c)** Stage III disease depicted by extrauterine disease. **(d)** Stage IVA disease with bladder or rectum involvement and distant organ spread of Stage IVB disease **(Shah and Ervine, 2020; Luna et al., 2021).**

Table (1): FIGO grading system for endometrioid carcinomas **(Mills, 2019)**

Grades	Pathologic findings
Grade 1	≤5% non-squamous solid growth
Grade 2	6–50% non-squamous solid growth
Grade 3	>50% non-squamous solid growth

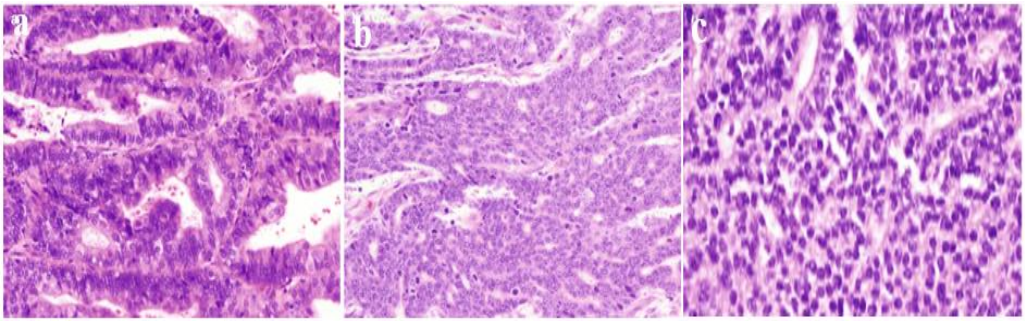

Figure (2): FIGO grading in endometrioid carcinoma is based on the contribution of solid, and non-squamous growth. (**a**) Grade 1 carcinomas demonstrate ≤5%, (**b**) Grade 2 carcinomas show 6–50%, and (**c**) Grade 3 carcinomas show >50% **(Mills, 2019)**.

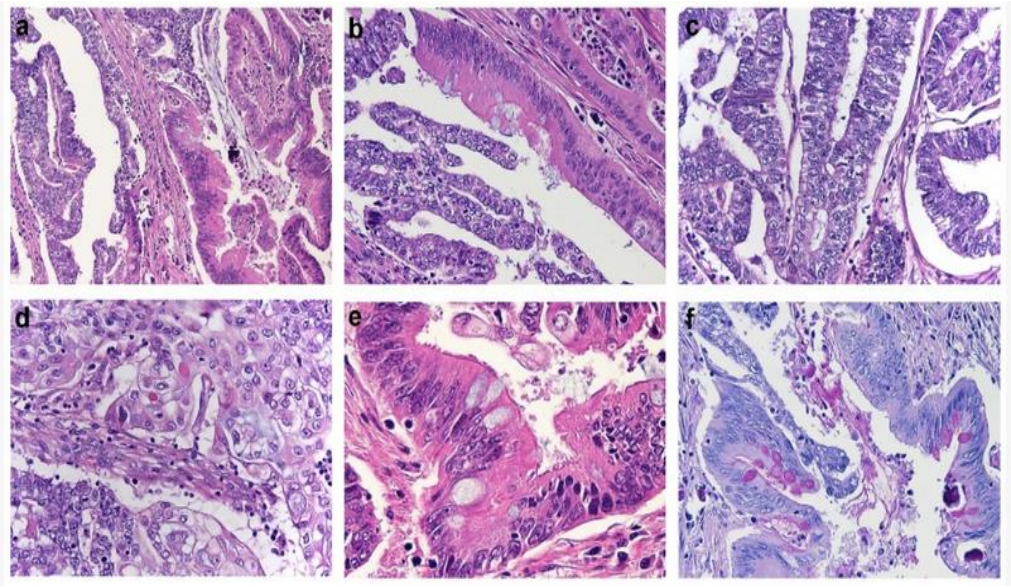

Figure (3): Histological features of EC showing intestinal-type features. **(a)** EC showing mixed endometrioid (right half) and intestinal-type mucinous (left half) features (H&E). **(b)** Single tumor gland showing concomitant endometrioid and intestinal-type differentiation (H&E). **(c and d)** Morphological details of the endometrioid component, composed by glands lined by columnar cells with scant cytoplasm **(c)**, and foci of squamous differentiation **(d)** (H&E). **(e)** Morphological details of the intestinal-type component composed by enterocyte-like cells with apical brush border and goblet cells (H&E). **(f)** Periodic acid–Schiff diastase **(**PAS-D) istochemical stain highlighting the presence of intracytoplasmic mucin in the goblet cells of the intestinal-type tumor component (PAS-D stain).

(A) Endometroid Adenocarcinoma:

Most endometrial cancers (90%) are adenocarcinomas that arise from uterine epithelial cells **(Kim et al., 2010).** These tumors are composed of glands that resemble normal endometrial glands. They have columnar cells with basally oriented nuclei, little or no intra cytoplasmic mucin, and smooth intra luminal surfaces. There is a complex glandular pattern and marked shift in glands to stroma ratio in favor of the glands, as tumor becomes less differentiated, they contain more solid areas, less glandular formation and more cytologic atypia. The well differentiated lesion may be difficult to separate from atypical hyperplasia **(Sivridis et al., 2013).**

(B) Papillary serous carcinoma:

Undifferentiated papillary serous carcinoma comprises approximately 5% to 10% of all endometrial cancers **(Mehasseb and Latimer, 2012).** Papillary serous carcinomas are all considered high-grade lesion. They are commonly admixed

with other histologic patterns, but mixed tumors behave as aggressive as pure serous carcinomas**.** Even when these tumors appear to be confined to the endometrium or endometrial polyps without myometrial or vascular invasion, they behave more aggressively than endometroid carcinoma, and have a propensity for intra-abdominal spread, simulating the behavior of ovarian carcinoma **(Lauren, 2018).**

(C) Clear cell carcinoma:

Although clear cell carcinoma accounts for only 4% of uterine cancers, it accounts for approximately 8% of uterine cancer related deaths **(Chung and Park, 2016).** Clear cell carcinoma characteristically occurs in older women and is a very aggressive type of EC. The prognosis is similar to or worse than that of papillary serous carcinoma. Overall survival rates of 33% to 64% have been reported. Myometrial invasion and lymph-vascular space invasion are important prognostic indicators **(Abdulfatah et al., 2017).**

(D) Mucinous carcinoma:

Endometrial carcinoma with mucinous histology comprises 0.6 to 5% of uterine cancers and is rarely found as a pure cell type. It is important to recognize mucinous carcinoma of the endometrium as an entity and to differentiate it from endocervical adenocarcinoma by the following features; the merging of the tumor with areas of normal endometrial tissue, presence of foamy endometrial stromal cells and presence of squamous metaplasia. Also the presence of areas of typical EC, and positive peri nuclear immunohistochemically staining with vimentin suggests an endometrial origin **(Jalloul et al., 2012).**

(E) Squamous carcinoma of the endometrium:

Squamous cell carcinoma is uncommon; it accounts for 0.1% to 0.5% of all uterine cancers. Squamous carcinoma of the endometrium is rare. Some tumors are pure, but most have few glands. This tumor has a poor prognosis with an estimated 36% survival rate in clinical stage I disease **(Pineda and Lurain, 2018).**

In order to establish primary origin within the endometrium; three criteria must be met:

- Adenocarcinoma is not present in the endometrium.
- The squamous carcinoma in the endometrium does not have any connection with the squamous epithelium of the cervix.
- Squamous carcinoma is not present in the cervix **(Wu et al., 2018).**

(F) Mixed types of carcinomas:

Endometrial carcinoma may show combinations of two or more of the pure types. The mixed types should be diagnosed in the presence of two or more distinct histological patterns, each of which accounts for at least 10% of total tumor volume **(Pineda and Lurain, 2018).**

(G) Undifferentiated carcinoma:

In 1 to 2 percent of endometrial cancers, there is no evidence of glandular, sarcomatous, or squmous differentiation. These undifferentiated tumors are characterized by proliferation of medium sized, monotonous epithelial cells growing in solid sheets with no specific pattern. Overall, the prognosis is worse than in women with poorly differentiated endometrioid adenocarcinoma **(Hoffman et al., 2012).**

5. Molecular mechanisms of EC invasion:

In 2013, The Cancer Genome Atlas Research Network (TCGA) reported that ECs could be divided into four groups of tumors based on the genomic analysis **(Kandoth et al., 2013).** Group 1 is the "POLE ultramutated" subgroup with very high mutational load and mutations in the exonuclease domain of polymerase-ε (POLE). Group 2 is characterized by "microsatellite instability" (MSI) frequently with high mutation rates ("hypermutated"). Group 3 is characterized by copy-number-low (CNL) subgroups with TP53-wild type and normal p53 expression ("endometrioid"), and group 4 is copy-number-high (CNH) with low mutation rates of TP53 mutations with aberrant p53 expression ("serous-like") **(Travaglino et al., 2020).** According to these classifications, progression-free survival of group 1 is most excellent followed by group 2 and 3, and group 4 is the worst **(Kandoth et al., 2013).**

Although TCGA classifications could provide better clinical prognosis compared to histological classifications, an easier and less expensive method has been developed using immunohistochemistry which is called Proactive

Molecular Risk Classifier for Endometrial Cancer (ProMisE) **(Talhouk et al., 2015).** ProMisE classifications showed four molecular groups of EC; POLE-mutated (POLEmt), mismatch repair-deficient (MMR-D), p53-abnormal (p53abn), and p53-wild-type (p53-wt). In recent years, correlations of conventional histological classifications and molecular classifications of TCGA or ProMisE have been reported. Summary of these molecular classifications and prognosis is shown in **Table (2) (Kobayashi, 2021).**

Table (2): Molecular classifications of endometrial cancers **(Kobayashi, 2021).**

The Cancer Genome Atlas (TCGA)	Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE)
POLE ultramutated	POLE-mutated (POLEmt)
MSI hypermutated	MMR-deficient (MMR-D)
Copy-number-low (endometrioid)	p53-abnormal (p53abn)
Copy-number-high (serous-like)	p53-wild type (p53-wt)

5.1. The PI3K–PTEN–AKT–mTOR pathway

Signal transduction via the PI3K–PTEN– AKT–mTOR pathway regulates cell growth, cell survival, protein synthesis, and metabolism. Molecular aberrations in this pathway occur in 80–95% of endometrioid carcinomas **(Kandoth et al., 2013)**. Somatic mutation of the PTEN tumor suppressor, which normally antagonizes PI3K pathway activation, occurs in 69–80% of endometrioid tumors and is the most common genomic aberration in this subtype **(Mcconechy et al., 2012)**. PTEN is present in a relatively large proportion of endometrial hyperplasia and congenital adrenal hyperplasia (CAH). PTEN mutation is an early event in the pathogenesis of endometrioid carcinoma. PTEN function loss in endometrial tumours is associated with elevated levels of phosphorylated protein kinase (AKT) via mutation, deletion, or loss of protein expression **(Cheung et al., 2011)**.

In addition to PTEN perturbations, somatic mutations in Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha and Phosphoinositide-3-kinase regulatory subunit 1 (PIK3CA and PIK3R1), which encode the PI3K, are also frequent in endometrioid carcinoma (40–56% and 20–43%, respectively) **(Cheung et al., 2011)**. Despite exceptions, PIK3CA and PIK3R1 mutations frequently co-occur with PTEN alterations, implying additive or synergistic effects. Individual PIK3CA mutations, however, can have different functional consequences depending on the protein domain in which they occur. This phenomenon is especially important in EC, which has a high frequency of PIK3CA mutations **(Bell and Ellenson, 2019)**.

Other mechanisms by which the PI3K–PTEN–AKT–mTOR pathway is dysregulated in endometrial tumors include inactivation of the tuberous sclerosis complex 2 (TSC2) and liver kinase B1 (LKB1) tumor suppressors. TSC2 or LKB1 protein expression loss has been reported in 13% and 21% of endometrioid carcinomas, respectively **(Lu et al., 2008)**. The concept that LKB1 inactivation is a factor of EC is assisted by mouse models in which LKB1 inactivation promotes tumorigenesis in the endometrium. Furthermore, conditional deletion of LKB1 and PTEN in the murine endometrium promotes endometrioid endometrial tumorigenesis **(Bell and Ellenson, 2019) (Figure 4).**

5.2. The RAS–RAF–MEK–ERK pathway and fibroblast growth factor receptor 2

The RAS–RAF–MEK–ERK pathway is a key regulator of cell proliferation, cell survival, and differentiation. The predominant mechanism of RAS–RAF–MEK–ERK pathway activation in endometrioid carcinoma is Kirsten rat

sarcoma virus (KRAS) mutation, which occurs in 15–24% of endometrioid tumors overall, and at a significantly higher frequency among endometrioid carcinomas **(Weigelt et al., 2013; Jones et al., 2017)**.

Most KRAS-mutated endometrioid carcinomas also have co-occurring alterations in PTEN, PIK3CA, and/or PIK3R1. Although there is crosstalk between the RAS–RAF–MEK–ERK and PI3K–AKT–mTOR pathways, KRAS mutation is associated with increased phosphorylation of MEK, and ERK, but not of AKT, in EC. KRAS mutation appears to be an imperfect predictor of MEK inhibitor sensitivity based on preclinical data. Endometrial cancer cell lines with concurrent KRAS mutation and PI3K pathway aberrations, for example, show variable sensitivity to MEK inhibition **(Weigelt et al., 2013)**.

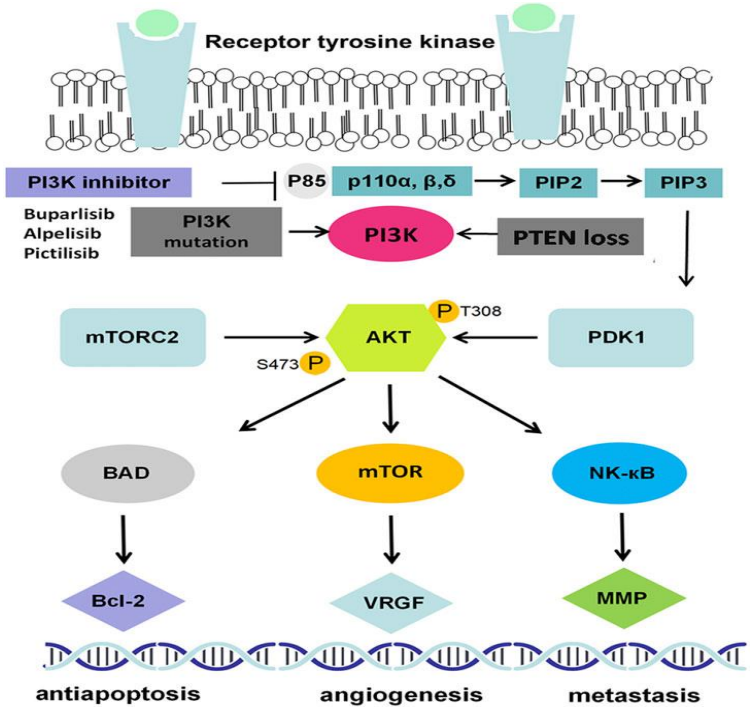

Figure (4): PI3K/AKT signaling pathway. PI3K: phosphatidylinositol 3-kinase; mTOR: mammalian target of rapamycin; NF-κB: nuclear factor kappa-B; MMP9: matrix metalloproteinase 9; VEGF: vascular endothelial growth factor **(Dong et al., 2021).**

5.3. The canonical WNT–β-catenin pathway

The canonical WNT–β-catenin pathway regulates a wide range of cellular processes, including cell proliferation, cell migration, cell survival, cell fate, and cell polarity. In endometrioid carcinomas, this pathway is often constitutively activated as a result of gain-of-function mutations in CTNNB1 (β-catenin), which prevent the phosphorylation and subsequent ubiquitin-mediated degradation of β-catenin. CTNNB1 mutations occur in 19–37% of endometrioid carcinomas overall **(Liu et al., 2014)**. There is almost complete mutual exclusivity between CTNNB1 mutations and KRAS mutations in endometrioid carcinomas, leading to the hypothesis that there is a crosstalk between the WNT–β-catenin and RAS–MAPK pathways, or alternatively, that dysregulation of these pathways converges on a shared biological process. Recent studies have identified significant associations between CTNNB1 mutations and poor outcome among low-risk endometrioid carcinoma patients, suggesting that CTNNB1 mutation has prognostic significance **(Stelloo et al., 2016; Kurnit et al., 2017)**.

Another way to disrupt the WNT—catenin pathway is through somatic mutation of Ring finger protein 43 (RNF43), a negative regulator of the pathway that targets the Frizzled receptor for ubiquitin-mediated degradation. In 18-27 % of endometrioid carcinomas, RNF43 is somatically mutated. However, unlike CTNNB1 mutations, RNF43 mutations are more common in endometrioid carcinomas **(Kinde et al., 2013) (Figure 5)**. Approximately two-

thirds of RNF43 mutations in endometrial cancer are frameshift mutations predicted to cause loss of function, consistent with the idea that RNF43 is a tumor suppressor **(Koo et al., 2012; Bell and Ellenson, 2019)**.

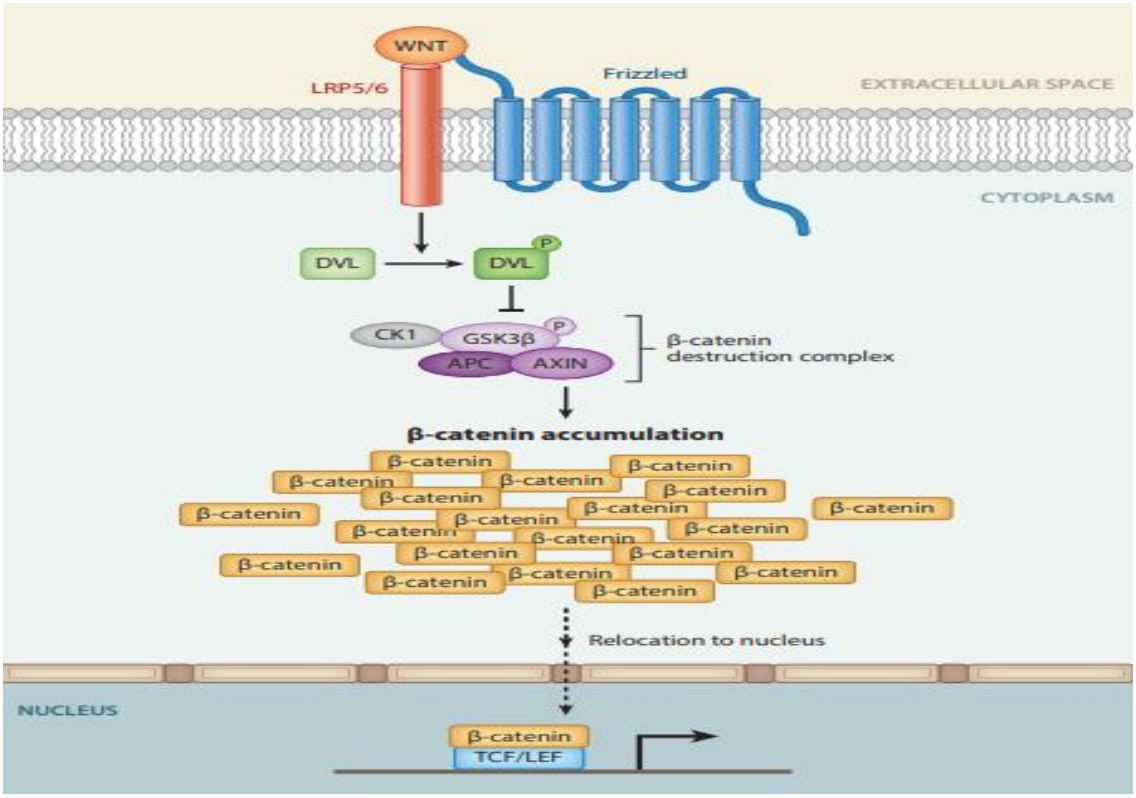

Figure (5): Overview of the canonical WNT–β-catenin pathway **(Bell and Ellenson, 2019)**.

6. Tumor markers in endometrial carcinoma

To improve prognosis, tumour markers must be identified for early detection of EC and for monitoring high-risk patients, such as those with severe obesity, diabetes, hypertension, Lynch syndrome, and PTEN gene defects. Because of an increase in EC incidence and mortality, tumor markers will be used to direct treatment, track therapeutic efficacy, and predict recurrence. Tumor markers are molecular substances found in blood, urine, or cancerous tissues. To date, no specific tumour markers with high sensitivity and specificity for diagnostic or prognostic purposes have been identified in EC **(Aksel and Çakir, 2020)**.

6.1. Human Epididymis Protein

Whey acidic protein (WFDC2), also known as HE4, is a promising cancer biomarker. It is found on chromosome 20 at 20q12-13 and is expressed in the reproductive tract as well as the respiratory epithelium. It is highly expressed in some cancer tissues. The US Food and Drug Administration (FDA) has approved it as a new tumour marker for epithelial ovarian cancer detection. Because EC is so similar to ovarian cancer, many studies are looking into HE4 as a marker **(Karlsen et al., 2014)**.

Mohammad et al. (2022) concluded that HE4 expression in both serum and tissue is a sensitive, specific diagnostic and prognostic biomarker in endometrial adenocarcinoma. Furthermore, it can predict extra-uterine involvement and disease staging **(Mohammad et al., 2022)**. However, the findings of **Cuesta-Guardiola et al. (2021)** concerning the utility of HE4 contrast with earlier reports. As they found poor correlation of tissue HE4 in patients with and without carcinoma. However, serum HE4 was significant for the diagnosis of EC; the conclusions for serum measurements are positive and suggest that the tumor marker HE4 seems to be able to diagnose EC **(Cuesta-Guardiola et al., 2021)**.

In a recent meta- analysis, high HE4 concentrations in patients with EC were found to be associated with shorter survival **(He et al., 2020)**. **Angioli et al. (2016)** found that patients can be classified as high or low risk of EC recurrence by using HE4 cutoff value.

6.2. Cancer Antigen 125

Cancer Antigen 125 **(**CA-125) is a glycoprotein found in tissues formed from mesothelial cells, such as the peritoneum, pleura, and pericardium, as well as tissues formed from cholemic epithelium, such as the endocervix, endometrium, and tubes. CA-125 is a tumour marker commonly used in the diagnosis and monitoring of epithelial ovarian cancer. The serum limit value is generally accepted to be 35 U/mL. CA-125 levels may also rise during physiological conditions like pregnancy and the menstrual cycle, as well as benign pathological conditions like endometriosis, pelvic infection, and uterine fibroids **(Aksel and Çakir, 2020)**.

There are also studies advocating that CA-125 can be used in the diagnosis of EC. A recent study found increased CA-125 levels in patients with EC when compared with normal controls. They have also determined that CA-125 was found to detect EC with 52.6% sensitivity and 80% specificity **(Nithin et al., 2018)**.

In a study of 393 patients with EC, CA-125 elevation was found to be a risk factor for pelvic lymph node metastasis, and preoperative serum CA-125 $\geq$ 27.6 U/mL remained as an independent risk factor for pelvic lymph node metastasis **(Li et al., 2019)**.

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

6.3. Cancer Antigen 19–9

Cancer Antigen 19–9 (CA 19–9) serum levels increase generally in gastrointestinal, lung, and ovarian cancer cases, but some studies have shown that CA 19–9 levels increase in EC cases. CA 19–9 levels are raised in 22–24% of the EC patients **(Ueda et al., 2010)**. Studies have found that the rise of serum levels of CA 19–9 is correlated with grade and FIGO stage **(Bian et al., 2017)**.

6.4. Carcinoembryonic Antigen

Carcinoembryonic Antigen (CEA) is a nonspecific gastrointestinal tumour marker that may increase in EC. CEA levels are elevated in 14-22 % of EC cases. Despite the fact that serum CEA levels differed significantly between cases with hepatic and pulmonary metastases, CEA levels were not sensitive or specific enough for EC diagnosis and follow-up **(Aksel and Çakir, 2020)**.

6.5. 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., 2014b; Kemik et al., 2016)**.

Fan et al. (2013) showed that YKL-40 levels were higher in EC patients than the control group and progression-free survival. In addition, overall survival rates were shorter in YKL-40 positive patients than YKL-40 negative patients. They also emphasized that YKL-40 can play an active role in the diagnosis and follow-up of EC (**Fan et al. 2013).**

6.6. Serum Amyloid A

Serum Amyloid A (SAA) is a high-density lipoprotein secreted primarily by the liver that plays an important role in the acute and chronic inflammatory processes. According to a recent meta-analysis study, high SAA levels are associated with a poor prognosis in solid tumours **(Lin et al., 2019)**.

In 2009, **Cocco et al. (2009)** reported the first evidence that high concentrations of SAA are present in the serum of uterine serous papillary carcinoma (USPC) patients. Moreover, they showed that elevated preoperative serum SAA levels can be useful in predicting more advaced stage and also to diagnose recurrence and response to treatment in USPC patients **(Cocco et al., 2009)**. They then reported in 2010 that endometrial endometrioid adenocarcinoma (EEC) cells expressed high levels of SAA, resulting in increased SAA concentrations in the circulation, and leading to a significant difference of SAA levels in healthy and benign disease subjects compared

to EEC patients. Furthermore, they discovered that grade 3 EEC patients have significantly higher SAA concentrations than grade 1 and 2 patients **(Cocco et al., 2010)**. At last, **Omer et al. (2013)** revealed that serum SAA levels in advanced EC patients were increased compared to healthy controls, and the cutoff point was 8.8 U/mL, with 68.7% sensitivity and 58.6% specificity. This cutoff value may be helpful for preoperative assessment and to plan ideal treatment for the patient **(Omer et al., 2013)**.

6.7. Neutrophil Gelatinase-Associated Lipocalin

Lipocalin-2, also known as neutrophil gelatinase-associated lipocalin, is a secretory protein with multiple biological effects that plays an important role in immune and inflammatory responses, tubular epithelial morphological transformation, and tumorigenesis **(Yu et al., 2014)**. It was shown that lipocalin-2 is highly expressed in gastric, breast, colorectal, and ovarian cancers; however, effects of it on endometrium have not been known adequately **(Aksel and Çakir, 2020)**.

Lipocalin-2 regulates insulin resistance and participates in the process of oncogenesis. It is associated with obesity which is a risk factor for EC **(Cabia et al., 2016)**.

Cymbaluk-Płoska et al. (2017) observed that lipocalin-2 expression was higher in EC patients compared to healthy endometrium and benign endometrial lesions. Also, lipocalin-2 levels and expression were found to be higher in grade 3 tumors, and advanced stages, and were associated with lymphovascular invasion and lymph node metastases **(Cymbaluk-Płoska et al. 2017)**.

Cymbaluk-Płoska et al. (2019) conducted another study on 123 patients with BMI > 21 kg/m^2 and showed that higher clinical staging of EC is associated with increase of lipocalin-2 concentration. Furthermore, they demostrated that the cutoff serum level of lipocalin-2 that distinguishes benign endometrial changes from EC is 160 ng/ml. The sensitivity of lipocalin-2 (84%) was higher than the sensitivity of the HE4 (66%) and CA125 (52%) markers for all women. The specificity of lipocalin-2 (80%) was slightly lower than HE4 (90%) for premenopausal patients, while the lipocalin-2 specificity (87%) was higher than HE4 specificity (85%) in postmenopausal women. In conclusion, the authors expected that lipocalin-2 with high sensitivity and comparable specificity to HE4 may be a useful biomarker in early detection of the EC **(Cymbaluk-Płoska et al. 2019)**.

6.8. Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) is a multifunctional growth factor that is particularly important in angiogenesis. VEGF is involved in a variety of physiological and pathological processes, including embryogenesis, wound healing, ocular neovascular diseases, and cancer. VEGF levels were found to be elevated in many cancer types, including lung, breast, colon, and melanoma **(Mahecha and Wang, 2017)**.

Many studies revealed that VEGF is associated with stage, myometrial invasion, lymphatic metastasis, and differentiation degree in EC **(Cai et al., 2017; Xu et al., 2018)**. VEGF levels were investigated in two pathologic EC types, and VEGF concentration was found to be associated with stage in Type II of EC but not in Type I **(Soufla et al., 2013)**.

7. Conclusion:

Endometrial carcinoma is one of most the common gynecologic malignancy. To date, no serum tumor marker was found in EC for diagnostic or prognostic purposes. Recent studies have concentrated on developing new potential biomarkers that will exhibit enough sensitivity and specificity in EC clinical practise. Understanding the prognosis of the patient would be helpful in determining his specific stage, grade, and histotype. The evolution of EC has been significantly influenced by both genetic and epigenetic changes. Understanding these modifications, particularly at the preneoplastic stage and grade, may help with early detection of EC. It is clear that population-based cohort studies are required to choose the best diagnosis and prognosis for EC.

8. Disclosure

None of the authors have any conflicts of interest.

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