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Review

Molecular bases of endometrial cancer: New roles for new actors in the diagnosis and the therapy of the disease

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ABSTRACT

Endometrial carcinoma (EC) is the most commonly diagnosed gynecologic malignancy in the western world. The majority of these cancers are curable, but a subset about 15–20% of endometrial tumors exhibits an aggressive phenotype.

Based on clinic-pathological and molecular characteristics, EC has been classified into two groups: Type I estrogen-dependent adenocarcinomas, which have a good prognosis and an endometrioid histology, and Type II or non-estrogen-dependent EC associated with poor prognosis and non-endometrioid histology. EC develops as a result of a stepwise accumulation of alterations that seem to be specific of each histological type. However, more knowledge is needed to better understand the differences in the biology and the clinical outcome of EC.

We would like to highlight the need to explore new potential biomarkers of EC as a tool for the detection and monitoring of aggressive endometrial tumors that, at the same time, will allow us to develop novel and more selective molecular targeted therapies against EC.

Contents

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1. Introduction

Endometrial carcinoma (EC) is the most commonly diagnosed gynecologic malignancy in the western countries with approximately 43,470 cases and 7950 estimated deaths recorded in 2010 in the United States alone (Society et al., 2010). Worldwide, EC is the fourth most common cancer in women. The incidence of this disease increases with age, particularly after menopause, with a median age at diagnosis of 61 years (Gracia et al., 2008; Sorosky, 2008). Around 90% of the cases are sporadic, while the remaining 10% arise from a genetic background.

Due to early clinical signs, such as abnormal uterine bleeding or spotting, especially in postmenopausal women, and early symptoms, such as pain during urination, intercourse or in the pelvic area, EC is often diagnosed in its early stages, when the disease is still confined to the uterus (≈75% of the cases) Amant et al., 2005; Network, 2009. However, there exists a subset of patients who suffer from a biologically aggressive strain of this disease, characterized by myometrial and lymphovascular invasion. For women with localized EC, the 5-year survival rate is around 96%; but, in cases where those women are diagnosed with cancer at the regional or distant stage, the survival rate dramatically decreases to 67% and 17%, respectively. These patients also have an increased risk of recurrence (Society et al., 2010).

The risk of EC is thought to be related to estrogen exposure, which increases the proliferative activity of endometrial cells, thus increasing the probability of the appearance of coding errors and somatic mutations (Park et al., 2008). Factors that increase estrogen exposure include the early onset of menstruation, late menopause, infertility, nulliparity, obesity, and menopausal estrogen therapy (without the use of progestin). Other risk factors, such as a history of polycystic ovary syndrome and Lynch Syndrome (or Hereditary Non-polyposis Colon Cancer – HNPCC), tamoxifen use, infertility and diabetes have been described (Watson and Lynch, 1993). An opposing effect, which seems to provide protection against EC, may be produced by pregnancy, the use of oral contraceptives, and physical activity.

Most endometrial malignancies (95%) develop in the endometrial glands and are referred to as endometrial carcinomas; the remaining 5% are mesenchymal tumors, carcinosarcomas and adenosarcomas (mixed epithelial/stromal tumors) (Park et al., 2008). In carcinosarcomas, two malignant components are observed, one epithelial (carcinoma) and one mesenchymal (sarcoma), which arise from the epithelial component. Classification of EC is made according to the International Federation of Gynecology and Obstetrics (FIGO) staging system.

Based on clinico-pathological and molecular characteristics, EC has been classified into two groups. The first is Type I or estrogen-dependent endometrioid endometrial carcinomas (EECs). This group represents the majority of patients with sporadic EC (approximately 80%), cases that arise in relatively younger pre- and post-menopausal women. It has been characterized by having a good prognosis, a low stage and low grade, and endometrioid histology. This type of tumor expresses estrogen (ER) and progesterone (PR) receptors and has a strong etiological association with estrogen exposure (Lax et al., 1998; Sherman et al., 1997). The second group consists of Type II or non-endometrioid endometrial carcinomas (NEECs). It is comprised of papillary serous and clear cell carcinomas, which have been associated with a poor prognosis, as well as a high stage and grade. They are usually negative or weakly positive for steroid hormone receptors. These cases arise in relatively older women and are not usually preceded by a history of unopposed estrogen exposure (Oehler et al., 2003). While NEECs arise from a background of atrophic endometrium, there exists both epidemiological and molecular evidence to suggest that endometrial hyperplasia may represent a precursor lesion to EEC. However, a classification of endometrial carcinoma within these two groups (Type I and Type II) is probably artificial; for this reason, this dualistic model has been challenged. Tumors, which are seen in daily practice, occasionally show overlapping or combined morphologic and molecular characteristics between them, in addition to ambiguous features.

Uterine corpus cancers are usually treated by surgery, radiation, hormones, and/or chemotherapy, depending on the stage of the disease. Specifically, patients with local EC, represented by FIGO stages I and II, undergo a standard of care that includes treatment by total hysterectomy and bilateral salpingo-oophorectomy. After surgical treatment, in cases where patients suffer from advanced EC, pelvic radiotherapy is used when deep myometrial invasion is observed and vaginal brachytherapy is administered when endocervical involvement is suspected. It is also of interest to note that adjuvant chemotherapy may improve the outcomes in selected patients after radical surgery. However, a standard of care is not well defined for patients with advanced stages of EC; thus, patients are traditionally treated using one or more combinations of surgery, chemotherapy and radiation. In the case of patients with recurrent or metastatic disease, where surgical resection is not recommended, traditional treatment has focused on chemotherapy. Inevitably, the prognosis of this last group of patients is dramatically poor with a decreased life expectancy, specifically, with a median survival of approximately 12 months (Fleming, 2007).

Although some genes and some molecular alterations are known to play an important role in the development of EC, the mechanisms that allow progression into an aggressive endometrial cancer phenotype are largely unknown. Moreover, the current treatment is not 100% curative, especially in those women who present advanced and recurrent EC. For these reasons, the characterization of new markers signaling the early steps of tumorigenesis, which are associated with the promotion of metastasis, would have significant clinical impact. In addition, the development of rational therapies, specifically directed against disseminated tumor cells and/or the implanted micrometastases, would also prove highly beneficial in the clinics.

2. Molecular genetics associated with endometrial carcinoma

Cancer development is characterized by self-sufficiency in growth signals, insensitivity to growth inhibition, evasion of apoptosis, angiogenesis, invasion and metastasis (Hanahan and

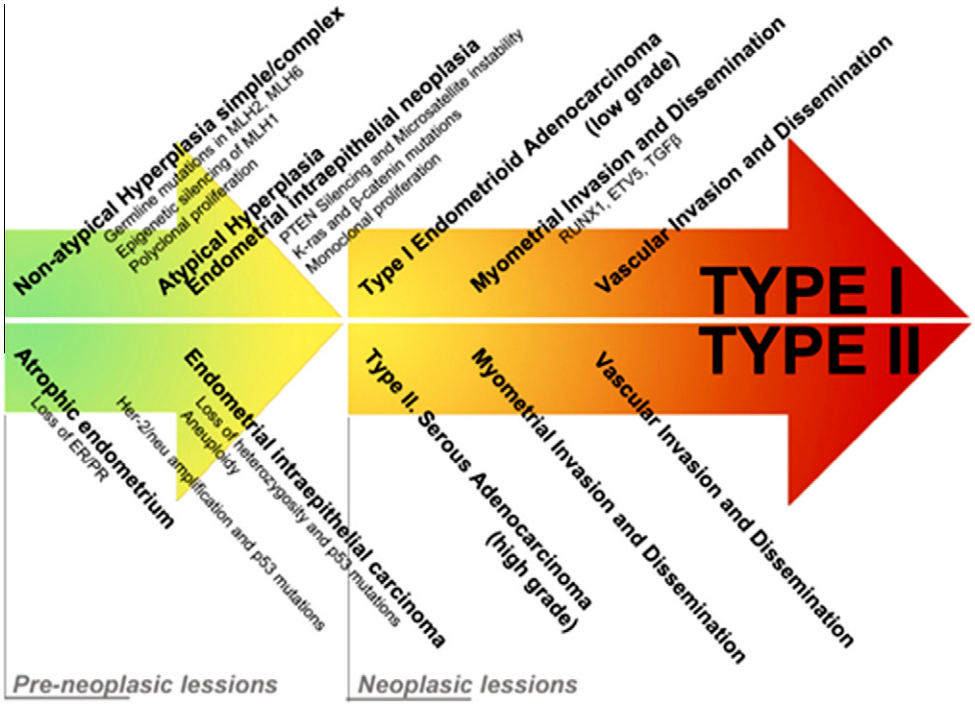

Fig. 1. Model of associated mutations during EC progression.

Weinberg, 2000). Like other malignancies, EC develops as a result of the stepwise accumulation of genetic alterations, which seem to be specific to each histological type.

The gradual elucidation of the molecular aspects of endometrial carcinogenesis has led to an association between Type I EC and alterations in the PTEN, PIK3CA, K-ras, β-catenin and/or DNA mismatch repair genes. Meanwhile, p53 mutations, STK15 and HER2/neu amplification, p16 over-expression and down-regulation or loss of E-cadherin, and also loss of heterozygosity (LOH) have been related to Type II EC (Fig. 1).

2.1. Molecular genetics associated with Type I or endometrioid endometrial carcinoma

Five molecular alterations have been described as a characteristic of endometrioid carcinomas; these are: microsatellite instability (MSI) and mutations in the PTEN, K-ras, PIK3CA and β-catenin genes. Most of the genetic alterations found in endometrioid carcinoma seem to occur very early in endometrioid tumorigenesis, although it is not clear which of these are associated with the earliest changes from malignant transformation and progression to neoplasia.

2.1.1. DNA-mismatch repair genes and microsatellite instability

DNA repair and the mismatch repair system (MMR) play a crucial role in promoting genetic stability. Microsatellites are simple, repetitive DNA sequences in the genome, which are susceptible to replication errors. MSI is a condition exhibited by damaged DNA, due to defects in the normal DNA repair process or during DNA replication, which are related to defects in the MMR genes. This causes the microsatellites to become unstable and can shorten or lengthen them, leading to the progressive accumulation of alterations on the DNA strand (Ionov et al., 1993). Mutations in some of the important regulatory genes may promote carcinogenesis and are known to play an important role in the development of different cancers.

The first abnormalities in DNA-mismatch repair genes were reported in the tumors of patients with hereditary non-polyposis colorectal carcinoma (HNPCC). In these cases, MSI arose from the DNA germ-line and from somatic mutations in one DNA-mismatch repair gene. There are several DNA-mismatch repair genes with different functions in humans. Some germ-line mutations of hMLH-2, MLH-1 and hMLH-6 have been described in EC (Taylor et al., 2006; Bianchi et al., 2006); even so, the most mismatch repair deficiencies underlying MSI in EC seem to involve epigenetic inactivation or silencing mechanisms. Indeed, the inactivation of MLH-1 through the hypermethylation of its promoter has been described as the most common cause of MSI in sporadic endometrioid EC (Esteller et al., 1997). Microsatellite instability has been reported to be less common in non-endometrioid cancers, displaying high grade features, than in endometrioid cancers (Prat et al., 2007; Catasus et al., 1998). MSI is found in 17–25% of all sporadic Type I ECs (Salvesen et al., 2000), but it is less frequently present in Type II tumors (Catasus et al., 1998; Tashiro et al., 1997).

In tumors with MSI, multiple heterozygous mutations in various genes located at different levels of the same signaling pathways may also result in the collapse of the equilibrium required for normal cell growth, cell survival, or DNA repair, associated with neoplastic transformation (Schwartz et al., 1999).

2.1.2. Oncogenes

A proto-oncogene is a normal gene that can become an oncogene, a tumor-inducing agent, due to mutations or increased expression. They code for proteins, called oncoproteins, which help to regulate cell growth and differentiation. For these reasons, they are often involved in signal transduction and the execution of mitogenic signals. Examples of proto-oncogenes include RAS, WNT, MYC, ERK, and TRK. Only a few oncogenes are altered in a substantial proportion of EC cases (Prat et al., 2007; Lax et al., 2000). Here, we comment on K-ras, Her-2/neu, PIK3CA, β-catenin and some other.

2.1.2.1. K-ras. The K-ras gene, which encodes the cellular membrane GTPase, functions as a molecular switch during cell signaling and has been largely related to tumor growth and differentiation. Mutations of this gene have been identified in 19–46% of ECs (Esteller et al., 1997). Alterations of K-ras predominately involve Type I tumors and have been reported in 10-30% of the cases of EC (Lax et al., 2000). Mutations are also detected in endometrial hyperplasia at a similar rate to that observed in EC, suggesting that mutations in the ras gene may represent an early event in tumorigenesis within a subset of Type I ECs (Sasaki et al., 1993). Different studies have shown that the frequency of K-ras mutations rises progressively from simple to complex hyperplasia and to carcinoma, and that the presence of K-ras mutations in pre-malignant biopsy samples has been suggested as a marker of progression to malignancy. Mutations in this gene have been associated with an adverse prognosis, independent of any clinicopathological, e.g. age at diagnosis, FIG0 stage, grade of differentiation, histological subtype and clinical status (Mammas et al., 2005; Doll et al., 2008).

2.1.2.2. HER-2/neu and downstream genes. HER-2/*neu*, also called erbB2 or HER2, is a member of the receptor tyrosine kinase (RTK) family, which is involved in cell proliferation via two downstream signaling pathways: the Ras-Raf-MAP kinase pathway and the phosphatidyl inositol-3-kinase (PI3K) and downstream protein serine/threonine kinase pathway (AKT) Cully et al., 2006. Overexpression of the protein product HER-2/neu is reported in 9–30% of all ECs, being more frequent in non-endometrioid tumors (Slomovitz et al., 2004; Berchuck et al., 1991). However, amplification in HER2 seems to be infrequent in EC and has been reported to be inconsistent with immunohistochemical over-expression (Slomovitz et al., 2004; Morrison et al., 2006).

In a study done in 90s the correlation between endometrial carcinoma and HER2/c-erbB2/neu was already found. Amplification of HER2 was examined in 50 endometrial carcinomas, 10 adenomatous hyperplasias and 50 normal endometrial samples, using the genomic differential polymerase chain reaction with the single copy reference gene interferon-gamma. It was found that HER2 was amplified in 14% of endometrial cancer patients which suggested a strong correlation between this genetic marker and an advanced disease stage (Esteller et al., 1995).

In a more recent study, this correlation is seen clearly. In EC advanced stages, HER2 amplification has been detected in 38% of clear cell carcinomas (3/8) and 28% of serous carcinomas (7/25), compared to7% of endometrioid adenocarcinomas (2/29). HER2 over-expression has been correlated with HER2 amplification ($r = 0.459$; $p < 0.0001$). In all stages of endometrial cancer, the rate of HER2 gene amplification was significantly higher in Type II EC compared to Type I EC (17% vs. 1%, $p < 0.001$). HER2 gene amplification was detected in 17% and 16% of the cases with uterine serous papillary and clear cell type histologies, respectively (Fleming et al., 2007).

2.1.2.3. PIK3CA. PIK3CA is the catalytic subunit of PI3K. Mutations in this gene occur in 24-36% of all cases and are coexistent with PTEN mutations in 14–26% of them (Oda et al., 2005). Studies have shown that PIK3CA mutations are frequent in EECs and are associated with invasion and adverse prognostic factors, such as blood vessel invasion (Catasus et al., 2008). However, PIK3CA mutations have also been described in Type II carcinomas. PIK3CA also plays an important role in the PI3K/AKT pathway's regulation of apoptosis. This fact suggests that its alteration could represent an important step in the development and progression of EC. Activation of this pathway suppresses apoptosis that is triggered by various stimuli. Recent analysis in EC, which integrated copy number and expression data, has shown that amplifications of PIK3CA correspond to expression profiles of PI3K activation; this suggests PI3K as a potential target for new therapies (Salvesen et al., 2009).

2.1.2.4. Beta-catenin. The beta-catenin gene (CTNNB1) is a component of the E-cadherin-catenin unit, which is very important for cell differentiation and the maintenance of normal tissue architecture. β-Catenin functions in a dual manner in epithelial cells, depending on the intracellular localization. At the plasma membrane β-catenin is an important component of adherens junctions, acting in cell-cell adhesion by linking E-cadherin, in conjunction with α-catenin, to the actin cytoskeleton. However, β-catenin can also act as the main effector of the canonical WNT signaling cascade in the nucleus (D'Souza-Schorey, 2005; MacDonald et al., 2009).

Beta-catenin is also important in signal transcription through the LEF/Tcf pathway. The APC protein down-regulates beta-catenin levels by cooperating with glycogen synthase kinase 3 beta (GSK-3beta).This induces the phosphorylation of serine-threonine residues coded in exon 3 of the beta catenin gene (CTNNB1), as well as its degradation through the ubiquitin-proteasome pathway. Mutations in exon 3 of beta-catenin result in stabilization of the protein, cytoplasmic and nuclear accumulation, participation in signal transduction, and transcriptional activation of genes involved in the development and progression of cancer. Mutations in exon 3 of CTNNB1 with nuclear accumulation of beta-catenin occur in 14–44% of all endometrial carcinomas and appear to be independent of the presence of MSI and the mutational status of PTEN and k-ras. There is a good correlation between CTNNB1 mutations and beta-catenin nuclear immunostaining, though occasionally, tumors may show nuclear staining in the absence of CTNNB1 mutations. There also exists controversial data regarding the prognostic significance of beta-catenin mutations in EC (Llobet et al., 2009).

Among the genes activated by β-catenin are factors associated with proliferation,such as cyclin D1 or c-myc, and genes associated with tumor cell survival and a tumor stem cell phenotype, such as survivin and MDR (Tetsu and McCormick, 1999; Shtutman et al., 1999; He et al., 1998; Zhang et al., 2001; Yamada et al., 2000; Fodde and Brabletz, 2007). These traits are necessary to give rise to a primary tumor during early stages of tumorigenesis, but insufficient to promote invasion and metastasis. Among the genes targeted by nuclear β-catenin and selectively expressed at the tumor-host interface are many of crucial importance to tumor invasion, such as L1CAM, CD44, TNC, VEGF, PLAUR, PLAU, MMP7, MMP14, LAMC2 and JUN. To invade the host stroma, tumor cells must loose epithelial differentiation and acquire a mesenchymal, motile phenotype. It is becoming evident that the interconnection of E-cadherin, β-catenin, and WNT signalling not only controls single events, but contributes to control the complex morphogenetic process of EMT. Loss of E-cadherin expression or loss of function of either APC, axin or GSK3β leads to a reduced degradation and subsequent overexpression of free cytoplasmic β-catenin, which can exert its nuclear function without control (Schmalhofer et al., 2009).

2.1.2.5. More oncogenes. Whereas the above-mentioned oncogenes have been well described in ECs, there are many additional proto-oncogenes under current investigation for their possible involvement in this disease. Some of them are c-myc, survivin, RUNX1, ETV5 (Ets-related protein) and human telomerase reverse transcriptase (hTERT) genes.

ETV5/ERM is a member of the PEA3 group of the Ets transcription factor family, which plays varied and important roles in development and tumorigenesis by up-regulating the expression of matrix-degrading proteases. Ets transcription factors are known to act as positive or negative regulators of the expression of genes

that are involved in various biological processes, including those that control cellular proliferation, differentiation, apoptosis, tissue remodelling, angiogenesis and transformation (Llaurado et al., 2011). It has been described that the Ets family transcription factor, ERM/ETV5, specifically is up-regulated in endometrioid endometrial carcinoma (EEC) and is associated with myometrial infiltration (Monge et al., 2007). ETV5/ERM binds to the consensus sequence, 5′-CGGA(AT)-3′. ETV5 is a proto-oncogene that has been described in the progression of breast cancer as an adaptor molecule in the interactions of adhesion receptors and intracellular tyrosine kinases, as well as in spermatogonial stem cell self-renewal (Monte et al., 1996; Chen et al., 2005). Like other Ets transcription factors, ETV5 has been found to take part in some chromosomal gene fusions, such as TMPRSS2:ETV5 and SLC45A3:ETV5 in prostate cancer (Helgeson et al., 2008).

In the case of EC, ETV5 has been proposed to play a role during the early events of endometrial tumorigenesis and could be associated with an initial switch to myometrial infiltration. Furthermore, it has been shown that ETV5 up-regulation may participate in the process of transition from normal atrophic endometrium to simple and complex hyperplasia and EC (Planaguma et al., 2004, 2005). ETV5 has also been related to regulating the migratory and invasive properties of the tumor and to increasing protective response against the oxidative stress produced in the promotion of an EC invasion (Monge et al., 2009). More recently, a codistribution of ETV5 with MMP-2 and MMP-9 has been reported at the invasive front of EC (Planaguma et al., 2011).

RUNX1/AML1 (runt-related transcription factor 1/acute myeloid leukemia 1) belongs to the RUNX gene family of transcription factors that bind DNA as components of the core-binding factor (CBF) complex in partnership with the CBFβ cofactor. This complex activates and represses the transcription of key regulators in the growth, survival and differentiation pathways.

The RUNX genes have been reported to function as both tumor suppressors and dominant oncogenes in a context-dependent manner. They are closely related and are essential for hematopoiesis, osteogenesis and neurogenesis (Blyth et al., 2005; Planaguma et al., 2006). Chromosomal translocations involving the RUNX1 gene are well-documented and have been associated with several types of leukemia.

In a microarray study of invasive EC, RUNX1 was identified as one of the most highly over-expressed genes (Planaguma et al., 2004), and through immunohistochemistry analysis, it showed a strong positive correlation to p21WAF1/CIP1 (a target of p53-mediated growth arrest), especially in carcinomas that had infiltrated more than 50% of the myometrium. It has been hypothesized that in EEC p21WAF1/CIP1 and RUNX1 could interact during the initial steps of tumor dissemination. Recent studies have reported a similar codistribution of MMP-2 and MMP-9, as with ETV5, at the invasive front of EC (Planaguma et al., 2011). Moreover, RUNX1 overexpression has been associated with the promotion of distant metastasis in an orthotopic EC mouse model (Doll et al., 2009).

2.1.3. Tumor suppressor genes

A tumor suppressor gene is a gene that protects cells from uncontrolled growth. When this gene is mutated (having a loss or reduction in its function), a cell can progress to cancer, usually in combination with other genetic changes. Tumor-suppressor genes, or the proteins for which they code, have a repressive effect on the regulation of the cell cycle and/or promote apoptosis.

2.1.3.1. PTEN. The tumor suppressor gene PTEN (phosphatase and tensin homolog deleted on chromosome ten) encodes for a phosphatase (with lipid and protein phosphatase activity) that antagonizes the PI3K/AKT pathway. Its activity may cause cell cycle arrest (Wu et al., 2003), the inhibition of focal adhesion formation, cell spreading and migration, as well as the inhibition of growth factor-stimulated MAPK signaling (Salvesen et al., 2001). As a result, the decreased activity or loss-of-function mutations of PTEN affect cell proliferation and survival, as well as increasing cell adhesion and migration (Cully et al., 2006; Boruban et al., 2008). PTEN has been reported to be altered in 25-83% of reported tumors, mainly due to mutations, rather than loss of heterozygosity (LOH) Simpkins et al., 1998. Up to 83% of these cases are endometrioid carcinomas, whereas serous and clear cell carcinomas harbor mutations in this gene in just 10% of the reported cases (Bansal et al., 2009; Mutter et al., 2000; Temkin and Fleming, 2009). Mutations in this gene have also been observed in endometrial hyperplasia, suggesting that this could be an early event in carcinogenesis (Maxwell et al., 1998). However, though still a subject of some controversy, PTEN mutations have been proposed to precede microsatellite instability (Latta and Chapman, 2002; Salvesen et al., 2004).

Mutations in the PTEN function, along with the consequent activation of the PI3K/AKT pathway, lead to the uncontrolled function of several kinases, such as mTOR, which acts as a promoter of cellular proliferation (Salvesen et al., 2001; Boruban et al., 2008). The activation of the PI3K/AKT/mTOR signaling pathway, induced by a loss of function of the PTEN gene, suggests that mTOR inhibition may play a therapeutic role.

2.1.3.2. p53. p53 is another tumor suppressor gene that prevents the propagation of cells with DNA damage. After DNA damage, the p53 protein accumulates in the nucleus and provokes cell cycle arrest by inhibiting cyclin-D1 phosphorylation of the Rb gene, thereby promoting apoptosis (Yin et al., 1999). The apoptotic index and p53 nuclear accumulation have been shown to be independent predictors of recurrence and short survival (de la Torre et al., 2007).

Alterations in this gene belong to the most common genetic features reported in various human neoplasms. Mutations in the p53 tumor suppressor oncogene are present in approximately 90% of all tumors and constitute the most common genetic alterations in Type II ECs. In contrast, p53 mutations have been observed in only 17% of the cases of endometrioid EC (Lax et al., 2000). p53 alterations play a minor role in clear cell type EC compared to serous type EC. p53 alterations play a relatively minor role in clear cell type endometrial carcinoma in comparison to the serous type (Lax et al., 1998). p53 mutations are also rarely observed in ovarian clear cells adenocarinomas in comparison to endometrioid adenocarcinomas (Okuda et al., 2003). As a result, it is possible that the pathogenesis of clear cell carcinoma in the female genital tract arises from a unique pathway (Zorn et al., 2005).

Due to the increased incidence of p53 mutations in serous carcinomas of the uterus, it is postulated that mutation in one allele may occur during the initial stages of neoplastic transformation, while loss of the second, normal allele may occur late in the progression to carcinoma (Mountzios et al., 2010).

2.1.3.3. ARID1A. ARID1A is a new identified tumor suppressor gene that is mutated in approximately 50% of ovarian clear cell and 30% of ovarian endometrioid carcinomas (Wiegand et al., 2010). Mutations in this gene have been associated with loss of protein expression (BAF250a) as assessed by immunohistochemistry. Recently, a large-scale analysis of a wide variety of carcinomas done by Guan et al. (2011), evaluated ARID1A immunoreactivity to determine the prevalence of ARID1A inactivation. Uterine low-grade endometrioid carcinomas showed a relatively high-frequency loss of ARID1A expression (26% cases; 40% of uterine endometrioid carcinomas). All mutations in endometrioid carcinomas were nonsense or insertion/deletion mutations, and tumors with ARID1A mutations showed complete loss or clonal loss of ARID1A expression. The other tumor that had a relatively high-frequency loss of ARID1A

expression was gastric carcinoma (11%). Their results suggest that the molecular pathogenesis of low-grade uterine endometrioid carcinoma is similar to that of ovarian low-grade endometrioid and clear cell carcinoma, tumors that have previously been shown to have a high-frequency loss of expression and mutation of ARID1A.

More recently, another work done by Wiegand et al. (2011) has also highlighted the importance of ARID1 in the endometrial carcinoma progression. In this case, immunohistochemistry for ARID1 was performed on tissue microarrays (TMAs) in more than 3000 cancers to determine whether the lost of this protein was common in other malignancies. Interestingly, it was found that loss of the protein ARID1 was frequent in endometrial carcinomas but infrequent in other types of malignancies, with loss observed in 29% of grade 1 or 2 and 39% of grade 3 endometrioid, 18% of serous and 26% of clear cell endometrial carcinomas. Moreover, all the hyperplasia cases showed expression of ARID1 as almost all the endometriosis atypical cases. In conclusion, loss of ARID1 expression is relatively common in high grade carcinomas arising from the endometrium, suggesting that ARID1A mutations can trigger malignant transformation.

Finally, Suh DH et al in the "Major clinical research advances in gynecologic cancer in 2010" point out the possible clinical impact of ARID1A targeting (Suh et al., 2010).

2.1.4. Apoptosis resistance

In EC, the deregulation of apoptosis is very important to tumor progression. Deregulation of apoptosis plays an important role in development and progression of cancer. Moreover, cells resistant to apoptosis are likely to escape the immune surveillance, but they may be also resistant to therapy. Apoptosis can be initiated by two main mechanisms: the intrinsic pathway, which has its origin in the mitochondria, and the extrinsic apoptotic pathway, triggered by the activation of death receptors situated in the cell surface. This last pathway is activated by tumor necrosis factor, Fas or TRAIL receptors which induce a seriate caspase activation, and an amplification of the apoptosis signalling. One of the key regulators of this signalling is c-FLIP. The instrinsic pathway is activated when the protein Bid is cleaved by one of the caspases activated and is then translocated to the mitochondria to activate this other apoptosis signaling pathway. Thus, these two apoptotic signalling pathways are connected (Llobet et al., 2009; Dolcet et al., 2005).

Several of the molecular abnormalities that have been detected in EC may be associated with apoptosis deregulation, suggesting its important role in EC progression. PTEN mutations lead to constitutively active Akt, which in turn suppresses the apoptosis triggered by various stimuli. Recent evidence that NF-kB activation is frequent in EC may explain the presence of apoptosis resistance by activation of target genes, such as FLIP and Bcl-XL (Dolcet et al., 2005; Pallares et al., 2004; Llobet et al., 2008a,b). Activation of the PI3K/AKT pathway suppresses apoptosis triggered by various stimuli. Moreover, the recent evidence that NF-ĸB activation is frequent in endometrial carcinoma may explain the presence of apoptosis resistance by activation of target genes such as FLIP or Bcl-XL (Pallares et al., 2004). Also members of the Bcl-2 family of genes are abnormal in EC. Finally, other proteins involved in apoptotic control (like survivin) have also been shown to be abnormal in endometrial carcinoma (Pallares et al., 2005).

An important protein responsible for apoptosis resistance in endometrial carcinoma is FLIP, which expression is frequent in endometrial carcinomas (Dolcet et al., 2005). A direct evidence of the role of FLIP in TRAIL apoptosis resistance on EC cells has been provided by treatment with specific siRNA targeting FLIP (Llobet et al., 2009). The transfected cells showed a marked decrease in cell viability, after TRAIL exposition. Moreover, Kinase suppressor of Ras 1 (KSR1) gene, which has been found overexpressed in EC, also regulates endometrial sensitivity to TRAIL by regulating FLIP levels (Llobet et al., 2011). Elucidation of the signaling pathways involved in apoptosis resistance will allow explanation of the various mechanisms for radioresistance in EC.

2.1.5. Epithelial to mesenchymal transition (EMT)

There is substantial evidence that in EC the development of the transition features from epithelial to mesenchymal may be associated with myometrial invasion which represents a determinant parameter highly valuable in prognosis (Monge et al., 2009). These features include a decrease in cell polarity and cell-to-cell contact, remodeling of the cytoskeleton, migratory phenotype and mesenchymal-like gene expression program. Under such circumstances cells show the increased expression of some genes, such as Snail, Twist, Slug and HMGA2, as well as the decreased expression of E-cadherin. Down-regulation of E-cadherin as a main player of epithelial to mesenchymal transition, as well as modifications on other molecules involved in cell-cell contacts, render cells with a migratory phenotype (Abal et al., 2007).

EMT can occur during myometrial invasion in some tumors, which show a distinctive morphological alteration characterized by the presence of microcystic, elongated and fragmented (MELF) glands.

MELF areas, compared to conventional glandular tumor areas, are usually negative for hormone receptors and show reduced E-cadherin expression. These findings suggest that a MELF-type invasion represents a specific tumor alteration consistent with EMT (Stewart and Little, 2009). In addition, the epithelial component undergoes a true epithelial-mesenchymal transition (EMT) in endometrial carcinosarcomas. The loss of epithelial characteristics, including cadherin switching and the acquisition of a mesenchymal phenotype, is achieved through changes in the miRNA expression profile, i.e., the down-regulation of the mir-200 family and the up-regulation of all the E-cadherin repressors (Snail, Twist, etc.) (Castilla et al., 2011).

3. Therapeutic strategies for endometrial carcinoma

3.1. Current treatments

Staging of uterine corpus tumors is accomplished according to a surgical system approved by the International Federation of Gynecology and Obstetrics (FIGO). The optimal staging of endometrial tumors would reflect their biology (intrinsic features of tumors, such as cell types and grades) and spreading patterns (uterine localization, depth of myometrial and/or lymphatic invasion, extrauterine spread, etc.), which would, in turn, allow for more accurate prognostication and also facilitate in therapeutic decision-making.

As such, the stratification of tumors aids in the selection of patient treatment, even though some of the features of the tumor within the uterus may still affect the prognosis for women with metastatic tumors. In addition, no single characteristic seems to represent an overwhelmingly dominant prognostic factor (Zaino, 2009).

Nowadays, the current treatments for EC are based on surgery, radiation therapy, hormone therapy, and chemotherapy, which may either be used alone or sequentially, in combination with other treatments, depending on disease stage and histological grade. The American College of Obstetricians and Gynecologists endorses full staging, including node dissection for all cases of EC (ACOG, 2005; Mariani et al., 2008); however, this last recommendation remains controversial.

Adjuvant treatment is commonly employed in advanced stages of the disease, and generally this treatment consists of chemotherapy,

radiotherapy, or a combination of both with decisions based on the presence of risk factors (Network, 2009; Dizon, 2010).

First-line chemotherapy typically consists of a combined regime, usually cisplatin/doxorubicin/paclitaxel, if tolerated, or cisplatin/doxorubicin or carboplatin/paclitaxel, followed by treatment with a single agent for disease progression.

Adjuvant chemotherapy has secured a place in the management of patients with advanced FIGO stage disease after radical surgery. However, therapy for advanced or recurrent endometrial adenocarcinoma still remains suboptimal with a mean survival that, in most situations, only measures from months to a few years. The poor survival of these patients underscores the need for new approaches to treatment and has prompted the clinical evaluation of novel drugs known to be active on other malignancies.

3.2. Molecular targeted therapy

Besides chemotherapy, agents that target specific molecular abnormalities have the potential to be used in second- and third-line therapies for EC. Based on experiences with other malignancies, these targeted agents typically have the greatest clinical impact when used in combination with chemotherapy.

There are several different signaling pathways that are good candidates for targeted therapy in EC (Llobet et al., 2009; Chon et al., 2006).

The PI3K pathway is the most frequently altered signaling pathway in endometrioid EC, often resulting from mutations in the tumor suppressor gene PTEN and activating mutations in PIK3CA. Because of the importance of this pathway in controlling survival, the use of PI3K inhibitors, such as wortmannin and its derivatives, raises the possibility that they may be potential anticancer agents.

An important AKT downstream effector is mTOR, as it regulates essential transduction pathways and is involved in coupling cell stimuli to cell cycle progression. mTOR inhibitors, based on rapamycin and it derivatives, have recently been developed as potential anticancer drugs. Some of the mTOR inhibitors have been tested in a PTEN+/− mouse model (Llobet et al., 2009; Podsypanina et al., 2001), and several of them, like temsirolimus, are currently being tested in two phase II trials in recurrent EC with promising results (Oza et al., 2008).

Tyrosine kinase receptors are also good targets for anticancer therapies. The epidermal growth factor family (EGFR or ErbB1, HER-2/neu or ErbB2, HER-3 or ErbB3, and HER-4 or ErbB4) and its growth factors are known to play critical roles in cell growth and differentiation. Oncogenic activation of tyrosine kinases is a common mechanism of carcinogenesis, and the druggable nature of these enzymes makes them attractive targets for therapy. Inhibitors of EGFR-mediated signal transduction include the monoclonal antibodies against EGFRs cetuximab (Erbitux®) and trastuzumab (Herceptin®) and the small molecule tyrosine kinase inhibitor lapatinib (GW572016). Despite their results in the clinical trials, there is merit in continuing to evaluate this class of drugs in women with EC (Gehrig and Bae-Jump, 2009; Fleming et al., 2003).

The vascular endothelial growth factor (VEGF) is another tyrosine kinase receptor that plays a key role in the angiogenic process and has been found highly expressed in endometrioid EC. The anti-VEGF monoclonal antibody bevacizumab has been tested in phase II trials, and the obtained results indicate that this drug has promising single-agent activity in women with recurrent or persistent EC. Another approach to blocking the effects of VEGF is the use of sunitinib, which inhibits multiple VEGF receptors. This drug is currently undergoing clinical trials to further explore its activity and safety (Dizon, 2010; Aghajanian et al., 2009). Finally, inhibitors of PARP have been proposed for targeting specific subtypes of EC, such as those exhibiting PTEN mutations.

4. New approaches in the diagnosis and treatment

4.1. Aspirates

EC is often diagnosed in its early stages, when the disease is still confined to the uterus; however there exists a subset of patients who have a biologically aggressive strain of this disease, which is characterized by myometrial and lymphovascular invasion. In these cases, the 5-year survival rate dramatically decreases. For this reason, new methods for prognosis and classification of EC are needed to fight against this deadly disease.

In the last few years, a number of studies on the detection and classification of uterine cancer have been conducted and reported in the literature. Sugiyama et al. reported some highly expressed genes in Type I and Type II cancers (Sugiyama et al., 2003). Using a cDNA array technique, they examine expression of more than 1000 cancer-related genes in endometrial cancer cells sampled from 21 tumors (10 cases type I and 11 cases type II EC), and they compared the expression patterns of the tumor cells with expression patterns of corresponding normal endometrial cells. They found 32 genes up-regulated and 58 down-regulated in cancer cells ($p < 0.05$). And between two types of EC, 45 genes highly expressed in type I and 24 in type II. P-cadherin was cancer specific, and vascular endothelial growth factor-C and MLH1 expression were limited to the type I and type II cancers, respectively. Risinger et al. reported distinct gene expression profiles among different histological subtypes of endometrial carcinomas using microarray analysis, with some genes exhibiting greater differences in expression between endometrioid and non-endometrioid ECs (Risinger et al., 2003). They examined global expression patterns of 42 endometrial samples (16 nonendometrioid cancers, 19 endometrioid cancers, and 7 age-matched normal endometria) using cDNA microarrays. They reported distinct gene expression profiles among different histological subtypes of ECs (24 transcripts could distinguish serous from endometrioid cancers, $p < 0.001$), with some genes exhibiting greater differences in expression between endometrioid and non-endometrioid ECs. Finally, they verify a subset of five genes (PEG3, STAT12, REV3L, FOXO1A, and MLLT7) in all tissue specimens using RTqPCR. In our group, we identified a number of genes associated with endometrial carcinogenesis (Planaguma et al., 2004). A work done by Planagumà et al. analyzed the differential gene expression profile between tumoral and nontumoral endometrial specimens with cDNA array hybridization. A number of genes associated with endometrial carcinogenesis were identified. Among the 53 genes for which expression was found to be altered in EEC, the acute myeloid leukemia proto-oncogene RUNX1/AML1 and the Ets transcription factor ETV5 were two of the most highly up-regulated. Additional studies have confirmed the upregulation of RUNX1/AML1 and ETV5 in endometrial cancer. The gene expression levels of RUNX1/AML1 and ETV5 were quantified by RTqPCR and verified using tissue array immunohistochemistry. The results demonstrated that the up-regulation of this gene in EEC correlated with the initial steps of myometrial infiltration (Planaguma et al., 2005). Yurkovetsky et al. identified that prolactin is a serum biomarker with sensitivity and specificity for endometrial cancer (Yurkovetsky et al., 2007). Others found that some serum proteins were more highly expressed in patients with Stage III disease as compared to those with Stage I, and a five-biomarker panel was presented, which discriminated endometrial cancer from ovarian and breast cancer. Nevertheless, none of these potential biomarkers have yet been validated or reached clinical practice.

The methods for detecting EC include pathology assessments on uterine aspirates, hysteroscopy-guided biopsies and the curettage method. Even though these methods are currently considered the

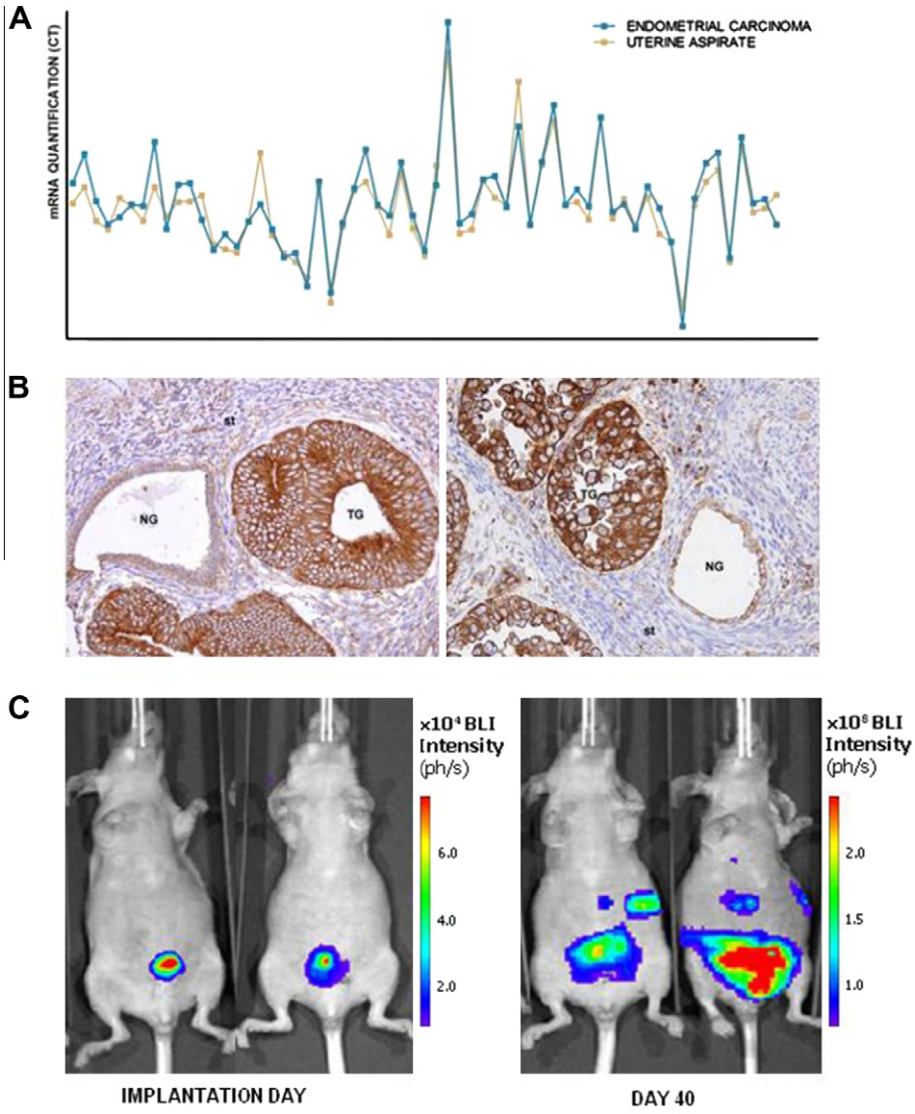

Fig. 2. (A) Analysis of Real Time-Q-PCR gene expression of the identified endometrial carcinoma markers in the primary tumor (blue) and the uterine aspirate (brown) of the same patient. On the *X*-axis, it is plotted each individual marker, and on *Y*-axis, gene expression is represented by the Cycle Thershold (*Ct*). (B) Immunohistochemistry of the marker P4HB in representative examples of endometrial carcinomas showing a specific staining at the tumoral glands. NG, normal gland; TG, tumoral gland; and ST, tumor stroma. (C) Images of an orthotopic mice model for endometrial cancer. In vivo BLI follow up of orthotopic Hec1A endometrial tumor progression and its metastatic dissemination.

gold standard for EC screening, they still have several drawbacks. First, they may cause significant discomfort. Second, as tools for diagnosis, they have only a moderate ability to predict a final pathology, and third, they require a trained pathologist for interpretation.

Recently, our group has been working on the identification and validation of new, potent molecular biomarkers for the detection of EC in uterine aspirates, as a fluid representative of the primary tumor (Fig 2A and B) (Colas et al., 2011). For this, gene expression screening on 52 carcinoma and 10 normal tissues was performed to identify potential biomarkers and were validated in an independent serie of 19 tissue samples by RTqPCR and on 50 carcinoma and non-carcinoma uterine aspirates. We found that the differential expression of these biomarkers in primary endometrial tumors is correlated to their expression level in corresponding uterine fluid samples and, we finally identified ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, SOCS2, and DCN as differentially expressed in ECs. These biomarkers significantly detected endometrial carcinoma with AUROC values ranging from 0.74 to 0.95, in uterine aspirates. Interestingly, analogous values were found to detect initial stages. The result of this study is a minimally invasive and highly sensitive and specific method for the identification of EC which will increase patient comfortability as actual methods of diagnosis are based in more invasive techniques and will provide a molecular, precise tool for supporting pathologist decision and hence, help gynecologists to reduce the number of unnecessary histeroscopies.

Among the various clinical applications for these newly discovered molecular biomarkers is a screening program within high-risk populations designed to improve the early detection of EC. At present, an ongoing clinical study on a large set of samples, collected at different hospitals, has being performed and their results will be published soon.

Finally, an ongoing clinical study on a large cohort of patients within several clinical institutions is currently evaluating the validity and clinical applications of this new diagnostic test for endometrial cancer.

4.2. The use of mouse models of EC

In EC, the precise molecular events that occur during development, progression, invasion and metastasis generation are uncharacterized. To better understand the EC molecular mechanisms and to improve clinical treatment, the use of clinically relevant mouse models, which fulfill tumor progression, invasion and metastasis, is an essential requirement.

Experimental models based on human EC cells are widely described (Du et al., 2009; Dai et al., 2005; Saidi et al., 2006; Wallace et al., 2009), mainly using subcutaneous xenografts. Although there is evidence that these models have helped us to understand the biology of tumors and have led to some therapeutic approaches to human cancer, they still have significant limitations, the most important of which is the different microenvironment of the tumoral implant from its original location.

In the last five years, few EC mouse models have been described. Kamat (Kamat et al., 2007) described an orthotopic EC model derived from Ishikawa and Hec1A cell lines transfected with luciferase. Both models produced metastatic implants. However, *in vivo* bioluminescence imaging (BLI) was only performed twice during the experiment, and the number of cells used was high (4×10^6).

A more recent model has been described by Takahashi in a study in which a highly metastatic model was needed (Takahashi et al., 2009). To generate a peritoneal dissemination endometrial model, Hec1A tumor cells were intraperitoneally injected into nude mice. To develop a lymph node metastasis model, tumor cells were injected into the uterine cavity of laparotomized mice, and to develop a lung metastasis model, cells were injected into the tail vein of nude mice.

Our group has been working on the development of subcutaneous and orthotopic murine models in EC (Doll et al., 2009), and recently, we have focused on the implementation of new tools, such as the use of BLI as a new technique to monitor and quantify tumor growth, progression and metastasis development, as well as a response to therapy in a non-invasive manner (O'Neill et al., 2010; Zhang et al., 2009). Using Hec1A cells, intrauterine implantation mimics the process of EC development, myometrial infiltration and metastasis generation. The use of the intrauterine implantation technique represents an advantage over our previously characterized mouse model (Doll et al., 2009), because the implant follows the natural infiltrative process from the inside to the outside the uterus (Fig. 2C). Moreover, *in vivo* BLI has enabled the direct observation of cancer cells spreading from their site of origin and arriving at secondary sites, longitudinally in time. The Hec1A cell line derived model represents advanced disease and can be used to test the efficacy of anti-metastatic drugs. We also have developed a second orthotopic EC model using human tumoral tissue, in order to keep the molecular phenotype and 3D structure. This type of model has never been described before in the literature. Orthotopically implanted, human endometrioid tissue produces myometrial infiltration, lymph-vascular invasion and dissemination in the pelvic cavity. It maintains the molecular and histological characteristics of the original samples, reproducing glandular patterns and expressing hormone receptors, as well as representing local and locally-advanced disease. This model could be complementary to the Hec1A cell line model for testing new anti-cancerous drugs, since it presents endometrioid EC histology. Finally, both models could be useful for studying how the process of metastatic appearance is influenced by gene expression (Cabrera et al., in press).

In conclusion, we have generated and characterized two different orthotopic EC murine models, which mimic the clinical behavior of cancer. These will provide an advanced tool for future studies dealing with tumoral physiopathology and the development of anti-cancer therapies and will serve as a useful tool in preclinical studies.

5. Conclusions

EC is a common malignancy that, despite its relatively good prognosis when diagnosed in its early stages, is responsible for many deaths in its advanced stages. It is evident that the transition from clinical staging to surgical-pathologic staging of tumors of the uterine corpus has represented a significant advance in prognostication and in determination of the need for additional therapy. Adjuvant chemotherapy has been shown to be useful in the management of patients with recurrent or advanced EC. However, many questions remain unanswered in terms of patient selection, the combination with adjuvant radiotherapy and the optimization of cytotoxic regimens in treated patients.

Since chemotherapy is the treatment of choice for patients with more advanced stages of the disease, the options available to women whose disease has progressed after their first-line therapy are limited. Novel, directed therapies, which target specific molecular abnormalities, have the potential to be used in second- and third-line therapies for EC. For this reason, they are currently under evaluation in this setting. Preclinical data suggest that it may be possible to improve on the activity achieved by previously used anticancer agents. Based on experiences from studies on other malignancies, an important clinical impact may be found by using these targeted agents in combination with chemotherapy.

The lack of biomarkers for endometrial cancer development and progression was identified as a key challenge in this field by the Epidemiology and Genetics Research Program (EGRP) at the National Cancer Institute (NCI) in their 2005 workshop. Fortunately, there has been significant progress in understanding the molecular bases for the malignant transformation of normal cells, and it is possible to take advantage of this increased understanding of tumorigenesis and develop novel therapies that target these molecular alterations.

The gradual elucidation of the diverse molecular pathways that govern the malignant phenotype in different types of EC may provide new and more individualized treatment options. Moreover, the appearance of novel molecular approaches, such as the detection of biomarkers in aspirates and more useful tools for therapeutic trials, such as the orthotopic mouse models, will improve the diagnosis, understanding and treatment of this disease. Specifically, the findings of novel molecular markers in aspirates will represent the basis for the development of a highly sensitive and specific, minimally invasive screening method for endometrial carcinomas. In addition, the improvement of EC mouse models, which mimic the clinical behavior of this cancer, will also provide an advanced tool for future studies dealing with tumoral physiopathology and testing for anti-cancer therapies in preclinical studies.

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