



Marguerite Bride. *Old Round Barn*. Watercolor, 11" × 15".

The molecular basis for the pathogenesis, classification, and implications for targeted therapies for endometrial cancer is reviewed.

The Molecular Biology of Endometrial Cancers and the Implications for Pathogenesis, Classification, and Targeted Therapies

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Background: Understanding and identifying molecular biology and genetics of endometrial cancer are central to the development of novel therapies. This article reviews the molecular basis for genesis of endometrial cancer with regard to pathogenesis, classification, and implications for targeted therapies.

Methods: Genes and cellular pathways that may have an important role in endometrial cancers, both endometrioid and nonendometrioid cancers, are identified. Recently studied drugs and potential future drugs that target some of these genes and pathways are reviewed.

Results: The most frequent genetic alteration of endometrioid endometrial cancer is *PTEN*. *PI3CA* and *K-ras* mutations are less common but are often associated with *PTEN*. Alterations in *MLH1* and *MSH6* are documented with microsatellite instability. β -catenin has a minor but significant association. Conversely, *p53* mutation is more often associated with nonendometrioid cancer; others being inactivation of *p16* and/or overexpression of *HER-2/neu*. Absence of *E-cadherin* is more often than not present in nonendometrioid cancers and is associated with poor prognosis. Novel agents that target the *AKT/PI3K-mTOR* pathway and those that inhibit epidermal growth factor receptor (*EGFR*), vascular endothelial growth factors (*VEGF*), fibroblast growth factor receptor 2 (*FGFR2*), and folate receptors are currently being investigated.

Conclusions: Novel targeted agents, either alone or in combination with cytotoxic agents, may result in superior treatment for patients.

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Introduction

Endometrial cancer is the most common gynecologic malignancy, with an estimated 40,100 new cases diagnosed in 2008.¹ Approximately 90% of cases of endometrial cancer are sporadic, whereas the remaining 10% of cases are hereditary.² A dualistic model of endometrial tumorigenesis is currently recognized, broadly termed type 1 and type 2, based on a classification system hypothesized by Bokhman³ in 1983. This model serves as a useful way to categorize these can-

cers in terms of both etiology and clinical behavior. It should be noted that this model is not entirely accurate in that a minority of endometrial cancers may exhibit shared characteristics. Also, the correct biologic and pathologic assignment of some uterine cancers is controversial, such as carcinosarcomas that may represent extremely poorly differentiated (ie, grade 4) endometrial cancers. These subjects are beyond this article and not reviewed here.

Type 1 endometrial cancers represent the majority of sporadic cases of endometrial cancer, accounting for 70% to 80% of new cases.³ These cancers are typically of endometrioid type and therefore are primarily associated with unopposed estrogen exposure. Risk factors include obesity, anovulation, nulliparity, and exogenous estrogen exposure. Type 1 endometrioid lesions arise in a background of hyperplasia and commonly express estrogen and progesterone receptors.³ Clinically, type 1 cancers are more often low-grade tumors with a favorable prognosis. In contrast, type 2 endometrial cancers are less common, accounting for 10% to 20% of endometrial cancers.^{4,5} They are often of nonendometrioid, high-grade histology, usually papillary serous or clear cell. Type 2 endometrial cancers are unrelated to estrogen exposure. Hormonal risk factors have not been

implicated in their pathogenesis, and type 2 cancers typically arise in a background of atrophic endometrium.³ Clinically, type 2 cancers are marked by an aggressive clinical course, and they have a propensity for early spread and poor prognosis.

Aside from their morphologic and clinical features, type 1 and type 2 endometrial cancers are further distinguished by genetic alterations (Fig 1). Endometrioid and nonendometrioid cancers are associated with mutations from independent sets of genes.⁶ Endometrioid endometrial carcinomas involve mutations in PTEN, K-ras, and β -catenin, as well as defects in DNA mismatch repair (Table).⁶ Nonendometrioid endometrial cancers frequently show aneuploidy and p53 mutations.⁶ This article reviews the molecular basis for endometrial tumorigenesis, with regard to pathogenesis, classification, and implications for targeted therapies.

Genetic Alterations of Type 1 Endometrial Cancers

Endometrioid carcinomas are characterized by a variety of genetic alterations, the most frequent of which is PTEN.^{7,8} PTEN has been reported to be altered in up to 83% of endometrioid carcinomas and 55% of precancerous lesions (Table).⁸ PTEN, located at chromosome

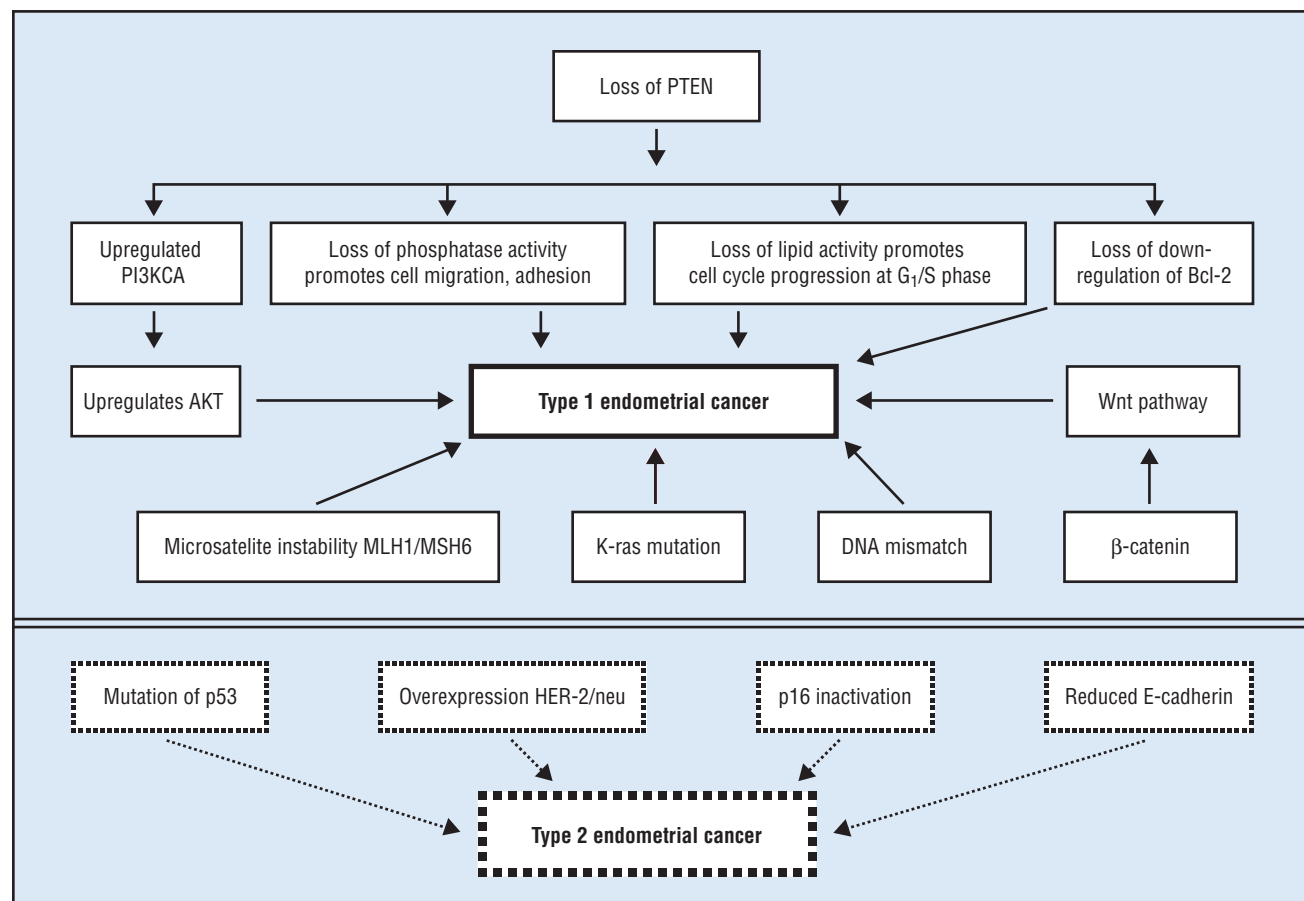


Fig 1. — Molecular basis of type 1 and type 2 endometrial cancers. Solid lines indicates type 1 causes and dashed lines indicate causes for type 2 endometrial cancers.

10q23, encodes a protein with tyrosine kinase function and behaves as a tumor suppressor gene. PTEN inactivation is caused by mutations that lead to a loss of expression and, to a lesser extent, by a loss of heterozygosity. The protein has both lipid and protein phosphatase activity, with each serving different functions. The lipid phosphatase activity of PTEN causes cell cycle arrest at the G₁/S checkpoint. Also, the upregulation of proapoptotic mechanisms involving AKT-dependent mechanisms is mediated through PTEN, as is the downregulation of antiapoptotic mechanisms through Bcl-2.⁹ PTEN further acts in opposition to phosphatidylinositol 3-kinase (PI3KCA) to control levels of phosphorylated AKT. Mutation of PTEN increases the PI3KCA activation, resulting in phosphorylation of AKT.¹⁰ PI3KCA mutation is seen in 36% of endometrioid endometrial cancers and is most common in tumors that also bear the PTEN mutation.¹¹ The protein phosphatase activity of PTEN is involved in the inhibition of focal adhesion formation, cell spread, and migration, as well as the inhibition of growth factor-stimulated MAPK signaling. Thus, loss or altered PTEN expression results in aberrant cell growth and apoptotic escape. Loss of PTEN is furthermore likely an early event in endometrial tumorigenesis, as evidenced by its presence in precancerous lesions, and is likely initiated in response to known hormonal risk factors. PTEN mutation is well documented in endometrial hyperplasia with and without atypia.¹² PTEN inactivation is most commonly caused by mutations in both alleles resulting in the complete loss of function.

Other genetic alterations in endometrioid endometrial cancers include microsatellite instability and specific mutations of K-ras and β -catenin genes. Microsatellite instability (MSI) has been demonstrated in 20% of sporadic endometrioid endometrial cancers.¹³ MSI refers to the propensity to develop changes in the number of repeat elements in microsatellites (ie, short segments of repetitive DNA bases found predominantly throughout noncoding DNA) compared with normal tissue due to DNA repair errors made during replication. Inactivation of any number of components of the mismatch repair system can lead to MSI. MLH1 inactivation is the most common mechanism in the endometrium and is accomplished by hypermethylation of CpG islands in the gene promoter. Inherited or somatically acquired mutations of MSH6, although relatively uncommon in endometrial cancers in general, are often seen in MSI endometrial cancers. MSI also represents an early event in endometrial carcinogenesis and has been demonstrated in precancerous lesions, likely targeting those genes that contain susceptible repeat elements. Interestingly, higher rates of mutations (60% to 80%) in the PTEN gene have been described in tumors with MSI

Table. — Genetic Alterations in Endometrial Cancer: Percentage Frequency of Genetic Mutations Identified in Type 1 and 2 Endometrial Cancers

Genetic Alteration	Type 1 Carcinoma (%)	Type 2 Carcinoma (%)
PTEN inactivation	50–80	10
K-ras mutation	15–30	0–5
β -catenin mutation	20–40	0–3
Microsatellite instability	20–40	0–5
p53 mutation	10–20	80–90
HER-2/neu	10–30	40–80
p16 inactivation	10	40
E-cadherin	10–20	60–90

compared to tumors without MSI (24% to 35%).¹⁴ Furthermore, the association between PTEN inactivation and MSI has been documented in type 1 endometrial cancer precursor lesions, suggesting that PTEN could be a target for mutations in a deficient DNA repair context. This also provides further support that these mutations play an early role in endometrial tumorigenesis.

Other genetic alterations documented in type 1 endometrial cancers include mutations in K-ras and β -catenin. K-ras mutations have been identified in 10% to 30% of type 1 endometrial cancers.⁴ Most studies (but not all) demonstrate a higher frequency of K-ras mutations in MSI cancers. Gain of function mutations in the β -catenin gene at 3p21 is seen in 25% to 38% of type 1 cancers as well.⁴ Whereas PTEN, MSI, and K-ras mutations often coexist with each other, mutations in β -catenin are usually seen alone.¹⁵ β -catenin, a component of the E-cadherin unit of proteins, is essential for cell differentiation and maintenance of normal tissue architecture, and plays an important role in signal transduction. β -catenin also acts as a downstream transcriptional activator in the Wnt signal transduction pathway. These mutations result in stabilization of protein that resists degradation, thus resulting in cytoplasmic and nuclear accumulation and constitutive target gene activity.² The accumulation of β -catenin has been demonstrated by immunohistochemistry. Several studies have analyzed endometrial cancers showing that nuclear accumulation of β -catenin is significantly more common in endometrioid lesions (31% to 47%) compared with nonendometrioid histology (0% to 3%).¹⁶ It has been suggested that nuclear accumulation rates could be attributable to abnormalities in other Wnt proteins, but the exact function of β -catenin in endometrial tumorigenesis remains unknown.² Alterations in β -catenin expression have also been demonstrated in atypical hyperplasia, thus representing an early event in endometrial tumorigenesis.¹⁶

Genetic Alterations in Type 2 Endometrial Cancers

The most common genetic alteration in type 2 serous carcinomas is in p53, the tumor suppressor gene.⁴ The

p53 gene is located on chromosome 17 and is important in preventing the propagation of cells with damaged DNA. Mutations in p53 are present in about 90% of serous carcinomas. The exact mechanism for the cause of this mutation is still unclear. After DNA damage, nuclear p53 accumulates and causes cell cycle arrest by inhibiting cyclin-D1 phosphorylation of the Rb gene and thereby promoting apoptosis.² Thus, mutated p53 results in a nonfunctional protein that accumulates in the cell and acts as a double negative inhibitor of the wild-type p53, leading to propagation of aberrant cells. Mutations in p53 are present in about 80% of endometrial intraepithelial carcinoma lesions, the putative precursor lesion to serous carcinomas. It is postulated that mutation in one allele occurs early during the development of serous carcinoma, and loss of the second normal allele occurs late in the progression to carcinoma.

Other frequent genetic alterations in type 2 endometrial cancers are inactivation of p16 and overexpression of HER-2/neu.² P16 inactivation was found in 45% of serous carcinomas and some clear cell cancers. The p16 tumor suppressor gene is located on chromosome 9p21 and encodes for a cell cycle regulatory protein. Thus, inactivation of p16 leads to uncontrolled cell growth. HER-2/neu overexpression and gene amplification were found in about 45% and 70% of serous carcinomas, respectively.¹⁷ HER-2/neu is an oncogene that codes for a transmembrane receptor tyrosine kinase involved in cell signaling. Negative and reduced E-cadherin expression occurred in 62% and 87% of serous and clear cell cancers, respectively. E-cadherin is a transmembrane protein with five extracellular domains and an intracellular domain that connects to the actin cytoskeleton through a complex with cytoplasmic catenin. Decreased expression of E-cadherin is associated with a loss of cell-cell cohesive forces and has been shown to precede tumor cell motility. E-cadherin negative tumors are more likely to be poorly differentiated or nonendometrioid and are associated with poorer prognosis.

Targeted Therapies

Advances in the understanding of molecular events leading to the development in endometrial cancer has led to the development of targeted anticancer therapies. Common targets for therapeutics include drugs that affect apoptosis, signal transduction, epigenetic modification, drug resistance, protein folding and degradation, cell cycle progression, hormone receptor activity, and angiogenesis. These new targeted agents are being investigated alone and with conventional therapy in the treatment of endometrial cancer. Fig 2 illustrates targeted pathways under investigation.

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase that is a central regulator of cell growth, proliferation, and apoptosis and is regulated

upstream by the AKT-PI3K-PTEN pathway. Potential therapies targeting the mTOR pathway include mTOR inhibitors, temsirolimus (CCI-779), everolimus (RAD001), and deforolimus (AP23573).¹⁷ Temsirolimus is a derivative of rapamycin and has demonstrated antitumor activity in a variety of preclinical human cancer models, including PTEN heterozygous mice with uterine cancer. Everolimus has the same mechanism of action as rapamycin, forming a complex with mTOR and the receptor protein FKBP-12 to inhibit downstream signaling events. Demonstrated activity in preclinical studies has led to numerous phase I and phase II trials in patients with recurrent endometrial cancer. In a phase II study of everolimus in 29 patients with recurrent endometrial cancer, a 44% clinical benefit response rate was found with single-agent treatment.¹⁸ Another phase II trial of temsirolimus in patients with metastatic and/or locally advanced recurrent endometrial cancer showed modest activity with temsirolimus, with a 7.4% partial response rate and 44% with stable disease.¹⁹ Another phase I trial of temsirolimus with topotecan (NCT00523432) in patients with gynecologic malignancies, including endometrial cancer, is currently recruiting patients. A trial of temsirolimus with and without megestrol acetate (Megace) and tamoxifen (NCT00729586) is planned, and a phase II trial of temsirolimus and bevacizumab (NCT00723255) is underway. A trial of everolimus with topotecan (NCT00703807) is also planned. A trial of deforolimus in patients with recurrent or persistent endometrial cancer (NCT00122343) has completed enrollment. A randomized phase II trial of deforolimus vs progesterone therapy for patients with one prior treatment (NCT00739830) is currently recruiting participants. A number of other agents targeting components of the mTOR-AKT-PI3K-PTEN pathway have also been developed, including enzastaurin (a PI3K inhibitor) and triciribine (an AKT inhibitor), that may be interesting to study in this disease.

Epothilone B analogs induce microtubule stabilization and are active against taxane-pretreated tumors.¹⁷ Ixabepilone (BMS-2474550) is a semisynthetic analog of epothilone B and is part of this new class of cytotoxic tubulin polymerization agents, which have different mechanisms of resistance than taxanes and thus remain sensitive in taxane resistant or insensitive tumors. A phase I trial of ixabepilone reported stable and minimal responses in patients with advanced ovarian and endometrial cancers.²⁰ A phase II study of ixabepilone in patients with recurrent or persistent endometrial adenocarcinoma (NCT00095979) is closed and results are awaited.

Epidermal growth factor receptor (EGFR) family members — ERBB1 (EGFR or HER-1), ERBB2 (HER-2/neu), ERBB3 (HER-3), and ERBB4 (HER-4) — have been shown to be highly expressed in endometrial cancers. Therefore, anti-EGFR targeted therapies are currently being investigated. Of all types of endometrial cancers,

60% to 80% overexpress EGFR, and 20% to 30% overexpress HER-2/neu.¹⁷ These agents result in downregulation of the MAPK and PI3K/AKT signal transduction pathways.¹⁷ Trastuzumab, a monoclonal antibody directed against HER-2/neu, has demonstrated activity in breast cancer when combined with cytotoxic agents. Unfortunately, GOG-0181-B investigated trastuzumab in advanced, recurrent, or persistent endometrial cancer, and preliminary results showed minimal activity, even in cancers with high overexpression of HER2/neu.²¹ Several other monoclonal antibodies targeting members of the ERBB/HER family, including pertuzumab, cetuximab, and panitumumab, are currently being investigated. Other agents such as gefitinib (ZD1839), erlotinib (OSI-774), canertinib (CI-1033), lapatinib (GW-572016), and imatinib (Gleevec;

STI-571) that act as small molecule inhibitors of the EGFR-TK pathway are also under investigation. A phase II trial of erlotinib in recurrent or metastatic endometrial cancer showed a response rate of 12.5% and showed erlotinib was well tolerated as a single agent.²²

Vascular endothelial growth factors (VEGF) and their receptors play a key role in normal and pathologic angiogenesis, and antiangiogenic agents have been developed to target this pathway. The successful activity of bevacizumab, a monoclonal antibody targeting VEGF in other solid tumors including endometrial cancer, has encouraged development of other agents.¹⁷ Sorafenib, a multitargeted kinase inhibitor with antiangiogenic activity, has been recently studied in advanced, recurrent endometrial cancer and carcinosarcomas.²³ Among 39 patients with uterine carcinomas,

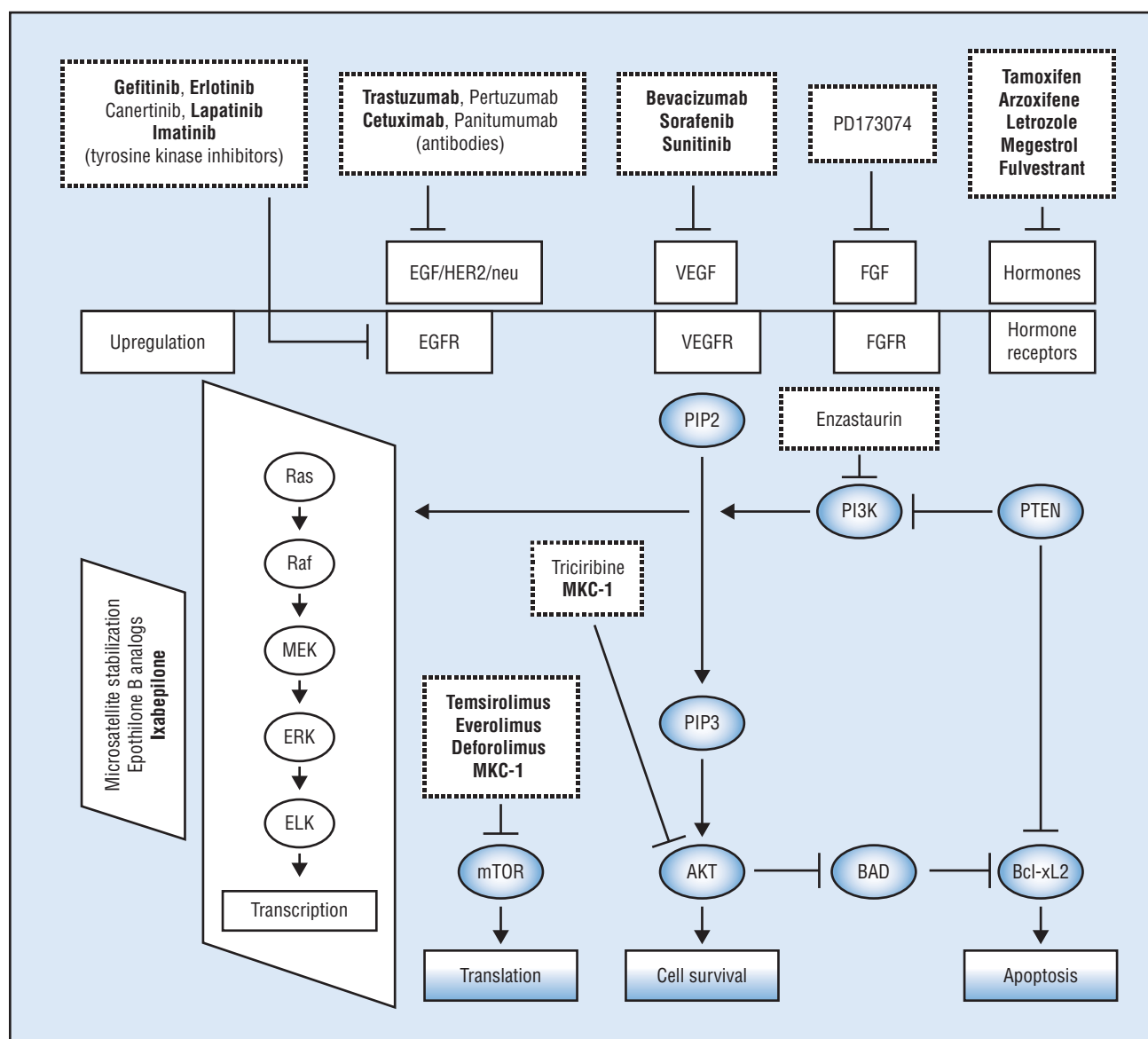


Fig 2. — This figure illustrates many of the cellular pathways currently being targeted in the treatment of endometrial cancer. Drugs that are bold type are in trials that are either ongoing or have already been completed. Solid lines and arrows indicate stimulation or upregulation of target gene or receptor; dashed lines and arrows indicate downregulation or inhibition of the target gene or receptors.

5% had a partial response and 50% has stable disease after 2 months of therapy. Results from this phase II study provide support for clinical benefit in advanced, recurrent uterine carcinomas.

Folate receptor alpha (FR- α) targeted therapy in high-risk endometrial carcinomas has been studied and found to be expressed in nonendometrioid, high-grade, and advanced-stage endometrial cancers, therefore making it an attractive therapeutic target.²⁴ An evaluation of a large cohort of high-risk endometrial cancer specimens found an association between FR- α expression and adverse outcome.²⁴ In vitro studies have also shown that tamoxifen upregulates FR- α expression; thus, estrogen negative cancers may also benefit from FR- α targeted therapy. This may be an attractive target for further clinical study.

Another proposed target lies in cells with an altered fibroblast growth factor receptor 2 (FGFR2) gene. In such cells, researchers at the Translational Genomics Research Institute (TGen) showed that a pan-FGFR inhibitor drug, PD173074, both inhibited growth and induced cell death.²⁵ The altered FGFR2 gene causes the receptors to become active, leading to cell proliferation. In an analysis of 116 primary endometrioid endometrial cancers, FGFR2 and K-ras mutations were mutually exclusive. FGFR2 mutations, on the other hand, were seen concomitantly with PTEN mutations. Molecular silencing of FGFR2 or treatment with PD173074 resulted in cell cycle arrest and induction of cell death in endometrial cancer cells with FGFR2-activating mutations. The FGFR2 inhibition led to cell death in those tumors that had a constitutively active AKT due to PTEN mutation. Therefore, although PTEN inactivation is a common event, the targeting of cancers with altered FGFR2 in this scenario may be part of the pathway to the future of personalized medicine.

Conclusions

Improved understanding of the molecular basis for endometrial cancer has led to the identification of molecular targets for novel therapeutic strategies of treatment. Numerous agents targeting different components have been developed and studied as single agents and also in combination with traditional cytotoxic agents. Additionally, molecular targeted therapies can be combined to deliver increased benefit to patients. Continued investigation into the molecular pathways of endometrial cancer development and progression will increase our knowledge of this disease process and will lead to the discovery of novel, superior treatment options for patients.

Disclosures

No significant relationship exists between the authors and the companies/organizations whose products or services may be referenced in this article.

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