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Future Directions and New Targets in Endometrial Cancer

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Abstract

Recent advances in next generation sequencing (NRG) have provided compelling evidence that endometrial cancers result from heterogeneous somatic mutations. These findings argue that a catalog of molecular aberrations that cause endometrial cancer is critical for the proper classification of these tumors and for developing novel and more effective targeted therapies against this disease. This chapter summarizes the recent advances made toward the elucidation of underlying pathway aberrations and the development of targeted therapies that exploit the unique molecular characteristics of endometrial cancers.

Keywords

Endometrial cancer • Uterine serous carcinoma • Targeted therapy • Immunotherapy • Novel therapies

Introduction

Endometrial cancers have historically been designated as Type I or Type II [1]. Type I endometrial cancer account for 65–70 % of cases and is associated with grade 1–2 endometrioid histology, younger age of onset, retention of estrogen receptor (ER), and progesterone receptor (PR) status, a history of unopposed estrogen, and deletions in k-Ras, PTEN, or mismatch repair mechanisms [2–4]. In contrast, Type II endometrial cancer is associated with serous, clear cell or grade 3 endometrioid histology, loss of ER/PR, black race, absence of unopposed estrogen, presentation at later stage, reduced

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E-cadherin expression, aneuploidy, mutations in p53, and HER2/Neu overexpression [5–9]. Type II endometrial cancer is typically more aggressive than type I cancer and has a poorer prognosis.

Recently, using an integrated genomic, epigenomic, transcriptomic, and proteomic approach, The Cancer Genome Atlas (TCGA) Research Network provided compelling evidence that endometrial cancers result from heterogeneous somatic mutations and, accordingly, classified endometrial cancers into four categories: (1) polymerase epsilon (POLε)-ultramutated, (2) microsatellite instability hypermutated, (3) copy-number low, and (4) copy-number high, serous-like [10]. The genetic aberrations of endometrial carcinomas may therefore represent a better tool to classify these tumors and guide adjuvant treatment for women harboring biologically aggressive disease. In this chapter, we discuss some of the new molecular pathways/targets identified in endometrial cancer and the state-of-the-art of both preclinical and clinical achievements in molecular-targeted therapy.

Molecular Pathways and Targets

Mismatch Repair Genes and POLε Mutations

Microsatellite instability (MSI), or alterations in the length of short repetitive deoxyribonucleic acid (DNA) sequences, is a result of the lack of intact DNA mismatch repair (MMR), which is an essential system for correcting DNA sequence errors during replication. The DNA MMR system may become disabled through intragenic mutations or promoter hypermethylation of one of the DNA MMR genes (e.g., *MLH1*, *MSH2*, *MSH6*, *PMS2*). POLε and polymerase δ (POLD) constitute the two nuclear DNA polymerases present in eukaryotic cells endowed with intrinsic proofreading activity [11, 12]. These polymerases are responsible for the bulk of chromosomal DNA synthesis during cell division, and multiple studies in yeast and mammalian cells have shown that polymerase proofreading and postreplication mismatch repair represent the primary guardians of DNA replication fidelity [11, 12]. In addition, loss of function in one or both of these genes dramatically increases the number of spontaneous mutations [11, 12]. Recent TCGA Research Network data demonstrated that 40 % of endometrial endometrioid tumors (i.e., Type I) and 2 % of the high-copy number serous-like tumors (i.e., Type II) are MSI hypermutated while about 10 % of endometrial cancers harbor POLε driver mutations [10]. In this study, MSI endometrial cancers were characterized by endometrioid histology, a lower MLH1 mRNA expression, and high frequency of somatic mutations (i.e., approximately tenfold greater than microsatellite stable (MSS) endometrial tumors) [10]. In contrast, POLε mutations were common in both type I and type II endometrial cancers [10, 12–14] and conferred an ultramutator phenotype that allowed incipient cancer cells to accumulate additional cancer-promoting mutations (i.e., the number of somatic mutations in POLε-mutated tumors exceed by far those found in MSI-mutated patients) [10]. Importantly, MSI hypermutated and POLε ultramutated endometrial cancer patients experienced a very good prognosis regardless of the fact that a large number of these patients harbored poorly differentiated endometrial tumors [10, 12–14]. It is currently not understood why patients developing MSI hypermutated or POLε ultramutated phenotypes may have such a good outcome; however, it is possible that the large number of somatic mutations present in these tumors may render these cancers highly immunogenic for the host due to the large number of mutated epitopes [15]. Thus, it may be unlikely to spread or metastasize due to their extremely high number of mutations [16]. Importantly, if the former hypothesis proves to be correct, the high mutation burden of these tumors, similar to what was recently demonstrated for melanoma and lung cancer patients, may confer clinical benefit to these patients if/when novel immunotherapeutic approaches based on blocking immune checkpoints antibodies (i.e., anti-CTLA4-ipilimumab, anti-PD1-nivolumab, Bristol

Meyers Squibb, Wallingford, CT) are implemented [17]. Alternatively, if the latter hypothesis is correct, as with breast and ovarian cancer patients harboring homologous recombination defects (i.e., BRCA1/2 mutations), synthetic lethality might be explored to develop targeted therapy effective in MSI and POLε-mutated endometrial cancers [18, 19].

Phosphatase and Tensin Homolog (PTEN) and Phosphatidylinositol-4, 5-Bisphosphate 3-Kinase, Catalytic Subunit Alpha (*PI3KCA*) and Regulatory Subunit (PI3KR1)

Cancer genetic studies suggest that the *Phosphatase and Tensin Homolog* (*PTEN*) and the *phosphatidylinositol 3-kinase* (*PI3K*) genes are two of the most frequently mutated genes in human tumors. TCGA data showed that up to 93 % of endometrial tumors had mutations in the PTEN/PI3K pathway suggesting the potential for targeted therapy with inhibitors against PI3K, AKT, or mTOR pathways in these tumors [10].

PTEN gene loss of activity is due to mutations in up to 61% [20–22] and due to a loss of heterozygosity in 40 % of cases [23]. PTEN protein acts as a lipid and protein phosphatase, and functions and behaves similar to a tumor suppressor gene. The lipid phosphatase activity of PTEN causes cell cycle arrest at the G1/S checkpoint; the protein phosphatase activity of PTEN is involved in the inhibition of adhesion formation, cell migration, and the inhibition of growth factor-stimulated MAPK signaling. PTEN protein also antagonizes the phosphatidylinositol 3-kinase (PI3K/AKT/mTOR) pathway by dephosphorylating phosphatidylinositol (3,4,5)-trisphosphate (PIP3). This dephosphorylation results in inhibition of AKT. Thus, loss of PTEN function leads to increased levels of phospho-AKT, activation of anti-apoptotic proteins, and ultimately an increase in cell cycle progression [24]. In atypical hyperplasia, PTEN inactivation occurs in up to 50 % of the cases. PTEN mutations are also found in simple hyperplasia and are partially associated with monoclonality [25]. Therefore, PTEN inactivation and mutations may be identified in endometrioid adenocarcinoma precursor lesions.

The *phosphatidylinositol-3-kinase* (*PI3KCA*) gene encodes for a heterodimeric protein with an 85-kDa regulatory subunit (PI3KR1) and a 110-kDa catalytic subunit (*PI3KCA*) [26, 27]. In endometrial cancers, unlike other human tumors, *PI3KCA* and PI3KR1 mutations are often associated with PTEN mutations. This is common in both type I and type II tumors [28]. PI3K phosphorylates a series of membrane phospholipids, catalyzing the transfer of ATP (adenosine triphosphate)-derived phosphate thereby forming secondary messenger lipids phosphatidylinositol-3,4-bisphosphate and phosphatidylinositol-3,4,5-trisphosphate [25–28]. PI3K plays a central role in cellular proliferation, growth, survival, mobility, and metabolism via activation of the PTEN/AKT pathway. PI3K is activated via the binding of a ligand to its cognate receptor, which attracts a series of kinases to the plasma membrane thereby initiating the downstream AKT/mTOR signaling cascade that regulates cell growth.

The central role of PI3K activation in tumor cell biology has prompted an effort to target PI3K and/or downstream kinases such as AKT and mammalian target of rapamycin (mTOR) in endometrial cancer. As a result, apitolisib (GDC-0980, Genentech, South San Francisco, CA), a potent inhibitor of class I PI3K and mTOR kinase (TORC1/2), has recently been tested in preclinical studies and not-surprisingly, has shown significant activity in vitro and in vivo against endometrial tumors harboring PI3K driver mutations [29]. Furthermore, AZD8055, a novel dual mTORC1/2 inhibitor, showed significant tumor growth inhibition in high HER-2/neu-expressor endometrial cancers in vitro [30] and caused in vivo regression in breast, lung, colon, prostate, and uterine xenograft models [31]. Taselisib, GDC-0032 (Genentech, South San Francisco, CA), a novel, oral, selective inhibitor of PI3K, has been shown to be highly active in vivo in uterine serous carcinoma (USC) mouse xenografts harboring *PI3KCA* mutations and overexpressing HER2/

neu ($p = 0.007$) [32]. Multiple phase I, II, and III clinical trials with inhibitors targeting PI3K, AKT, or mTOR pathways are currently ongoing or have been recently completed [33]. Unfortunately, emerging clinical data show limited single-agent activity of such inhibitors at tolerated doses [34–36]. However, it is important to note that the response rate for patients with heavily pretreated, advanced cancers and *PI3KCA* mutations who were given PI3K/AKT/mTOR axis inhibitors was significantly higher than that for patients without documented *PI3KCA* mutations treated on the same trials [36]. This observation is consistent with data that demonstrate low response rates on traditional phase I and II trials, in which molecular testing is not used, and suggests that selecting *PI3KCA*-mutant patients for treatment with PI3K/AKT/mTOR axis inhibitors may potentially predict response. Taken together, these results imply that screening for *PI3KCA* and PI3KR1 mutations may warrant further investigation in the application of targeted PI3K/AKT/mTOR inhibitors to the clinic in endometrial cancer patients.

Epidermal Growth Factor Receptor (*EGFR*; ErbB-1; HER1)

The ErbB receptor tyrosine kinase family consists of four cell surface receptors: ErbB-1 or epidermal growth factor receptor (*EGFR*) or HER1, ErbB2 or HER2/neu, ErbB-3, and ErbB4. Type I tumors are more likely to exhibit mutations in *EGFR* when compared to Type II tumors (46 % versus 34 %) [37]. *EGFR* is a membrane receptor that lies upstream to the PI3K/AKT/mTOR and Ras-Raf-MEK-ERK pathways. After ligand binding, *EGFR* becomes active as a homodimer. It may also pair with another member of the ErbB receptor family, such as ErbB2/Her2/neu, and become an activated heterodimer. In type II tumors, *EGFR* expression correlates with survival ($p = 0.028$) [38]. Therefore, *EGFR* is a therapeutic target of significant interest.

As reported by Schwab et al., the tyrosine kinase inhibitors (TKI) afatinib (Gilotrif™, Boehringer Ingelheim, Ridgefield, CT) and neratinib (Puma Biotechnology, Los Angeles, CA) both exhibit significant tumor growth inhibition both in vitro and in vivo models of USC harboring overexpression of *EGFR* and HER2/neu [39, 40]. In addition, in vivo models showed improved survival when using both agents independently. Afatinib works by covalently binding to intracellular phosphorylation sites of ErbB1, ErbB2, and ErbB4, as well as inhibiting transphosphorylation of ErbB3. Neratinib is an irreversible inhibitor of ErbB1 and HER2/neu, and prevents activation of the signaling pathways brought about by receptor dimerization.

HER2/neu (ErbB-2)

The HER2 protein has a cysteine-rich extracellular ligand-binding domain, a hydrophobic membrane-spanning region, and an intracellular tyrosine kinase domain. In HER2-amplified cells, there may be up to 100 *C-ErBB2* gene copies per tumor cell [41] compared with two copies present in normal cells. This overamplification results in HER2 overexpression at both the mRNA and protein levels and a resultant phosphorylation of intracellular tyrosine kinase residues [42]. This modulates cell proliferation, differentiation, migration, and survival in addition to upregulating the Ras/Raf/MAPK and PI3K/AKT/mTOR pathways. In many solid tumors, HER2 expression status is now determined using immunohistochemistry (IHC), and fluorescence in situ hybridization (FISH) assays in instances of equivocal IHC results, though no standard guidelines exist for HER2 testing in endometrial cancer [43]. HER2 overexpression correlates with prognosis [44]. Thus, given that up to 69 % of all endometrial cancers and up to 80 % of type II endometrial tumors overexpress HER2, it is an important molecular target for therapy.

Trastuzumab (Herceptin®, Genentech, South San Francisco, CA) is an FDA-approved

HER2-targeting antibody that is approved for use as an adjuvant in early-stage, HER2-positive, node-positive breast cancer [45]. There have been multiple encouraging case reports using trastuzumab in USC [46–48], and the effect on progression-free survival in advanced or recurrent USC is currently being evaluated in a multi-institutional phase II trial of trastuzumab combined with paclitaxel and carboplatin compared with paclitaxel and carboplatin alone [49]. Pertuzumab (Omnitarg®, Genentech, South San Francisco, CA) is a humanized IgG1 monoclonal antibody heterodimerization inhibitor that binds domain II of the ErbB2 receptor. When compared to trastuzumab, pertuzumab inhibits broader downstream signal transduction pathways through abrogation of lateral signal transduction [50–52]. Lapatinib (Tykerb®, GlaxoSmithKlein, Philadelphia, PA), a reversible dual inhibitor of both HER2 and *EGFR*, has shown the ability to restore trastuzumab sensitivity in cells that have previously shown resistance to trastuzumab therapy [53]. As clinical trials move forward, these agents will play a significant role in targeted therapy.

Trastuzumab is also used as a vehicle in the antibody-drug-conjugate trastuzumab emtansine (Kadcyla®, T-DM1, Genentech, South San Francisco, CA). DM1 belongs to the maytansine class of cytotoxic agents. T-DM1 is internalized by HER2 receptor-mediated endocytosis, offering selective effects on HER2-overexpressing cells. After internalization, T-DM1 is degraded by lysosomes, resulting in the release of free intracellular DM1. DM1 is a microtubule assembly inhibitor and its action leads to cell death as a result of G2/M phase cell cycle arrest. [54, 55] T-DM1 also has action similar to trastuzumab alone with regard to reducing signaling in the HER2 pathway and initiation of antibody-dependent cell-mediated cytotoxicity [56–58]. In 2014, English et al. showed significant activity of T-DM1 in vitro and in vivo in USC [59]. T-DM1 was more effective than trastuzumab in inhibiting cell proliferation and causing apoptosis ($p = 0.004$) in USC overexpressing HER2. T-DM1 was highly active at reducing tumor formation in USC xenografts overexpressing HER2 ($p = 0.04$) and mice treated with TDM-1 had significantly longer survival when compared to mice treated with trastuzumab alone and untreated control mice ($p \leq 0.0001$). These are promising results that will undoubtedly be further evaluated in clinical trials.

Vascular Endothelial Growth Factor (VEGF)

When the core of a tumor attains a critical level of hypoxia, neoangiogenesis occurs as an effort to promote tumor growth, progression, and metastasis. Vascular endothelial growth factor (VEGF) enhances vascular permeability, vasodilation, and capillary fenestration and is a prime target for modulation. The VEGF family consists of six members: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and PIGF and their respective receptors (VEGFR) [60]. In endometrial cancer, VEGF-A overexpression is a poor prognostic indicator and is associated with advanced grade, lymphovascular space invasion and spread [61, 62], and upregulation of p53 [63].

Bevacizumab (Avastin®, Genentech, South San Francisco, CA) is a recombinant IgG1 monoclonal antibody that neutralizes VEGF and has shown promising results in multiple phase II trials for recurrent endometrial adenocarcinoma. For example, in Gynecologic Oncology Group (GOG) trials 229G and 229E, bevacizumab was used alone [64] and in combination with temsirolimus [65], respectively. As a standalone treatment of 15 mg/kg every 3 weeks in patients with two or three prior lines of chemotherapy, bevacizumab exhibited a 13.5 % response rate [64]. Bevacizumab, 10 mg/kg given biweekly as a combination with temsirolimus 25 mg weekly, showed improved outcomes; 24.5 % of patients exhibited a clinical response and 46.9 % of patients achieved a progression free survival of 6 months or more [65]. A three-arm randomized phase II study of paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, and ixabepilone/carboplatin/bevacizumab as initial therapy for measurable stage III/IV or recurrent endometrial

cancer is ongoing [66]. The results of this study are eagerly awaited by the oncology community.

Other VEGF-related therapies are being developed as well. VEGF Trap (Eylea®, afibercept, Sanofi-Aventis, Paris, France) is a monocolonal IgG fusion protein that serves as a decoy receptor for VEGFR-1 and -2; ramucirumab (Cyramza®, Eli Lilly, Indianapolis, IN) is a mononcolonal antibody that targets VEGFR-2. In a phase II study of 44 women with recurrent or persistent uterine cancer using aflibercept, 6-month progression-free survival was 41 % and overall response rate was 7 % (all partial responses); there were two treatment-related deaths due to gastrointestinal perforation and arterial rupture [67]. While not yet reported in endometrial adenocarcinomas, Cyramza® yielded promising improvements in progression-free survival relative to placebo in the phase III REGARD trial in patients with locally advanced or metastatic gastric or GE junction adenocarcinoma who had progressed on or after prior fluoropyrimidine- or platinum-containing chemotherapy [68]. Powell et al. recently reported a response rate of 18.6 % in patients with recurrent or persistent endometrial carcinoma who received brivaniv, an oral dual anti-VEGF and weak anti-fibroblast growth factor receptor (FGFR) agent [69].

FBXW7/Cyclin E/PPP2RA1

In uterine serous carcinoma, whole-exome and Sanger sequencing have revealed mutations in *FBXW7* (19 %) and *PPP2R1A* (18 %) in both carcinomas and matched precursor endometrial intraepithelial carcinoma [70]. FBXW7 is an F-box protein that is critical in the ubiquitination of the tumor-promoting proteins cyclin E and PPP2R1A [71–73]. *CCNE1* encodes cyclin E1, the upregulation of which promotes cell cycle progression through the G1 phase via interactions with CDK-1 [71]. PPP2R1A is a regulatory unit of serine/threonine protein phosphatase 2, which regulates growth. In USC, mutations in *PPP2R1A* have been reported in up to 32 % of tumors and somatic amplifications of *CCNE1* were identified in up to 44 % [74–76]. Cyclin-dependent kinase inhibitors may have a role for use in USC. In addition, curcumin has been proposed as a regulator of the proteasome and cyclin family of cell cycle proteins [77], yielding yet another potential therapeutic intervention.

Skp2 E3 Ligase Inhibitors

The F-box protein, Skp2, a component of the SCF-Skp2/Cks1 E3 ligase complex, has specificity for the tumor suppressor and cyclin-dependent kinase inhibitor, $p27^{kip1}$ (p27) causing its ubiquitylation and subsequent degradation by the 26S proteasome [78, 79]. Normally, the levels of p27 increase in the nucleus and bind to and inactivate CyclinE/Cdk2 maintaining the retinoblastoma protein (pRb) in a hypophosphorylated state for cell cycle arrest [80]. Accordingly, p27 nuclear expression is low in proliferative phase endometrium and high in the secretory phase [81–84]. In endometrial cancer and other cancers, there is a statistically significant decrease in p27 with a concomitant increase in Skp2 [85–88]. This loss of p27 is caused by its perpetual degradation in the nucleus due to high Skp2/Cks1 E3 ligase activity ultimately leading to uncontrolled proliferation [89]. Knocking down Skp2 in endometrial cancer cell lines completely obviates estrogen-induced degradation of p27 and growth stimulation. Moreover, estrogen causes MAPK-dependent phosphorylation of p27 on threonine 187, which is essential for its identification and ubiquitylation by SCF-Skp2/Cks1 [89]. These results purport a pathogenic mechanism for estrogen-induced type I endometrial cancer, representing 85 % of uterine cancers and thus, blocking nuclear p27 degradation by Skp2/Cks1 is a rational molecular target for this cancer [90, 91].

Whereas unopposed estrogen increases the risk for developing endometrial hyperplasia, the precursor to type I endometrial cancer [91], ostensibly due to degradation of p27, progesterone treatment increases the level of nuclear p27

with concomitant inhibition of proliferation in primary endometrial cancer cells [84, 89]. Progesterone therapy (Megace®) for hyperplasia and cancer is associated with an increase in nuclear p27 [92, 93], thereby underscoring the significance of p27 as a molecular target forendometrial growth. Of note, the PTEN tumor suppressor and p27, which both negatively control cell cycle progression, malfunction as an early event in endometrial cancer oncogenesis [94], and it has been shown that Skp2 functions in the regulation of p27 and cell proliferation by the PTEN/PI3K pathway [95]. Rather than regulation of cell proliferation by transcription and translation [89], the studies point to the Ubiquitin Proteasome System as the essential regulator of normal and malignant endometrial epithelial cell growth supporting the use of proteasome inhibitors as a rational therapeutic approach for endometrial cancer and others with loss of p27 due to high Skp2/Cks1 E3 ligase activity.

The first general proteasome inhibitor for cancer therapy, bortezomib (Velcade, PS-431) was approved for multiple myeloma [96], but is marginally effective and failed for other cancers because they ostensibly blocked the degradation of both oncogenes and tumor suppressors [97]. Aided by X-ray crystallographic studies, Skp2 and Cks1 of the SCF complex form a structural druggable pocket where p27 is ubiquitylate [98–100]. Computational ligand docking of the structure of the interface between Skp2/Cks1 and p27, and a virtual ligand screen (VLS) was used to identify small molecule inhibitors that specifically block degradation of p27 phosphorylated on Threonine 187 [100]. Unlike other SCF-Skp2 complexes that target a variety of proteins for degradation, importantly, the pocket formed by Skp2/Cks1 has substrate specificity for ubiquitylating only the cyclin-dependent kinase inhibitors p27 and p21 [99]. Another means for disabling p27 from arresting cell growth is its sequestration in the cytoplasm in some cancers including endometrial cancer [87, 101, 102]. Cytoplasmic mislocalization occurs when p27 is phosphorylated on threonine 157 by Akt kinase activity. This aligns with the loss of PTEN phosphatase function in blocking PI3K/Akt in endometrial cancers [91]. In the cytoplasm, p27 not only loses its nuclear antiproliferative effect but assumes an oncogenic phenotype mediating migration/metastasis [101, 102]. Fortuitously, certain Skp2 inhibitors increase nuclear p27 while decreasing cytoplasmic p27 in endometrial carcinoma patient primary cells [103]. Thus, these inhibitors might have dual therapeutic advantages as both cytostatic as well as anti-metastatic agents.

In vitro, the novel small molecule inhibitors of Skp2/Cks1 E3 ligase activity, named Skp2E3LIs, block phosphorylation of pRb, the downstream molecular target for cell cycle arrest in G1 and stabilize nuclear p27 by markedly increasing its half-life [103]. Skp2E3LIs blocked both estrogen stimulation of proliferation and degradation of nuclear p27 to the same extent as blocking estrogen receptor activation with ICI 182,780. In vivo, Skp2E3LIs injected into estrogen-primed mice, obviated estrogen-induced hyperplasia, increased nuclear p27, and decreased the number of mitotic endometrial epithelial cells by 62 % [103]. These studies provide functional proof of principle that Skp2E3LIs act in the nucleus to prevent estrogen-induced degradation of p27 thereby regaining growth control by directly blocking Skp2/Cks1 ubiquitylation. The activity in mice suggests that the Skp2E3LIs might have utility in the treatment of complex atypical endometrial hyperplasia to prevent the development of endometrial carcinoma. Human endometrial cancer xenograft studies in immunocompromised mice using genetically defined patient cells with respect to PTEN, Akt, *PI3KCA*, Her2 amplification/mutations, are underway with the current Skp2E3LIs. Together with screening for Skp2 levels, these studies should aid in tailoring patient-specific Skp2E3LI therapy while these compounds are clinically developed.

The apparent critical importance and enthusiasm for developing specific inhibitors of Skp2 E3ligase activity to advance the field by supplanting the current non-specific anti-proteasome therapy has been shared by others [104, 105]. In one study, a Skp2 inhibitor discovered through a high throughput in silico screen was shown to suppress human prostate and lung

cancer xenograft growth in immunocompromised mice [106]. The Skp2E3LIs are distinguished from other Skp2 inhibitors as they stabilize p27 in the nucleus to prevent cell cycle progression by pharmacologically targeting the binding interaction between the E3 ligase, SCF-Skp2/Cks1, and p27 [106]. As an advantage for endometrial carcinoma prevention and therapy, Skp2E3LIs target the etiologic agent for this cancer by stabilizing p27 in the presence of estrogen. Moreover, Sp2E3LIs subvert the need for progesterone receptors, lacking in higher grade cancers that cannot respond to progestin therapy.

Claudins

Claudins are membrane proteins that are involved in the formation of tight junctions, which block the diffusion of protein and lipids through the plasma membrane [68, 69], and which are associated with epithelial breakdown. They also assist in recruiting cell-signaling proteins, regulate cell proliferation, cell differentiation, and neoplastic transformation [107]. One of the extracellular loops of the claudins acts a binding site for *Clostridium perfringens* toxin (CPE) [108]. Claudin-3 is a low-affinity receptor for CPE, and claudin-4 is a high-affinity receptor for CPE. Claudin-3 and -4 have been found to be among the highest differentially expressed genes in USC [109], in addition to a variety of other cancers [110, 111]. Claudin-3 and -4 may represent markers for biological aggressiveness; in one study of 20 USC samples, CPE receptors were identified in 100 % of samples and significantly higher levels ($p < 0.05$) in metastatic USC when compared with primary tumor sites. Thus, USC that are recurrent or refractory to standard treatments may be susceptible to CPE-based therapeutic approaches.

Tubulin

Class III β-tubulin heterodimerizes with α-tubulin to form microtubules critical to cell division. Resistance to paclitaxel has been tied to the upregulation of class III β-tubulin [112], and loss of PTEN appears to confer enhanced tubulin-based metastatic cell reattachment [113]. Paclitaxel binds preferentially to class I β-tubulin [114], and higher class III β-tubulin expression reduces the rate of microtubule assembly, rendering cells less susceptible to paclitaxel [115]. Aggressive histologic subtypes of gynecologic cancer, such as USC, clear cell carcinomas, and other solid tumors, have been associated with high levels of class III β-tubulin [116–118].

Epothilones are microtubule-stabilizing macrolides isolated from the bacteria *Sorangium cellulosum* [119], which exhibit activity against paclitaxel-resistant malignancies due in part to equal binding affinity for class I and class III β-tubulin [120]. Patupilone (Novartis, Basel, Switzerland) and ixabepilone (Ixempra®/BMS-247550; Bristol-Meyers-Squibb, NY, USA) are notable members. In vitro, patupilone has shown good efficacy in the inhibition of tumor cell growth in uterine cancer cell lines [117, 121, 122]. Ixabepilone has shown activity at the phase II level for advanced or recurrent endometrial adenocarcinomas [123], but not for uterine leiomyosarcomas previously treated with a taxane [124]. Importantly, class III β-tubulin has not yet been shown to be upregulated in leiomyosarcoma. Ixabepilone remains under evaluation as first-line therapy with carboplatin and bevacizumab in stage III/IV primary or recurrent endometrial cancer.

Future Directions

Recent reports on the genetic landscape of somatic single-nucleotide and copy-number mutations in endometrial cancers have greatly contributed to a deeper understanding of the molecular aberrations underlying these tumors and provided opportunities for genome-guided clinical trials. Novel immunotherapy approaches based on immune checkpoint-antibodies in hypermutated and ultramutated tumors and tumor-specific drug delivery; small molecule inhibitors against PI3K, AKT, or mTOR

pathways; anti-angiogenic and novel cytotoxic agents such as the epothilones against MSS and biologically aggressive copy-number high; serous-like endometrial tumors are among the most promising developments for this disease. With growing recognition of the importance of individual tumor biology, in the next few years, we hope that targeted therapies will allow for the genuine practice of personalized molecular medicine in endometrial cancer.

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