Chapter 11

Hormonal Heterogeneity of Endometrial Cancer

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Abstract

Endometrial cancer is the most common malignant tumor of the female genital tract in the developed world. Increasing evidence suggests that the majority of cases can be divided into two different types of endometrial cancer based on clinico-pathological and molecular characteristics. Type I is associated with an endocrine milieu of estrogen predominance. These tumors are of endometroid histology and develop from endometrial hyperplasia. They have good prognosis and are sensitive to endocrine treatment. Type II endometrial cancers are not associated with a history of unopposed estrogens and develop from the atrophic endometrium of elderly women. Mainly, they are of serous papillary or clear cell morphology, have a poor prognosis and do not react to endocrine treatment. Both types of endometrial cancer probably differ markedly with regard to the molecular mechanisms of transformation. The transition from normal endometrium to a malignant tumor is thought to involve a stepwise accumulation of alterations in cellular mechanisms leading to dysfunctional cell growth. This chapter reviews the current knowledge of the molecular mechanisms commonly associated with development of type I and type II endometrial cancer.

Introduction

With 142,000 new cases every year, endometrial cancer (EC) is worldwide the seventh most frequent carcinoma of women. About 42,000 women die of this malignancy every year. In the developed world EC is the most common malignancy of the female genital tract and the fourth most common malignancy in women. In the Western industrialized countries, annual incidence rates between 10 per 100,000 women (U.K, Spain, France) and 25 per 100,000 women (U.S.A, Canada) are observed.[1,2] Though the curability of EC is high, tumors with particular morphological variants, adverse histopathological features and /or advanced stage are characterized by aggressive behavior and poor prognosis.

Increasing evidence suggests that at least two different types of EC exist. Type I is associated with an endocrine milieu of estrogen predominance. It frequently develops via a characteristic sequence of hyperplastic lesions of the endometrium with increasing premalignant potential. These tumors have a favorable prognosis.[3] On the molecular level mutations of the *ras*-oncogene, loss of *PTEN* tumor suppressor gene expression and dysfunction of DNA-mismatch repair genes are involved.[4,5] Additional mutations (e.g., in the *p53* tumor suppressor gene, loss of estrogen and/or progesterone receptor expression) are typical features of a further malignant transformation to aggressive, dedifferentiated endometrioid endometrial carcinomas with poor prognosis.[4,5]

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About 10% of endometrial cancers are type II lesions. Type II EC is not associated with systemic hyperestrogenism and typically develops from the atrophic endometrium of elderly women. The histological type is either poorly differentiated endometrioid or non-endometrioid. The initial molecular event for the development of type II EC is probably a mutation of *p53* resulting in intraepithelial endometrial cancer which rapidly progresses to invasive serous-papillary carcinoma or other high-risk types of endometrial cancer. Sex steroid hormones are probably not involved in the tumorogenesis of these highly aggressive EC.[4,5]

However, the molecular mechanisms involved in development of EC remain poorly understood. This chapter reviews the current knowledge of the molecular mechanisms commonly associated with development of type I and type II EC.

Etiology

Type I and type II EC differ substantially with respect to etiology, pathogenesis and clinical behavior. For details see Table 1.[2,5]

Type I EC is driven by continuous exposure to estrogens in the absence of sufficient levels of progestogens. Typical risk factors are obesity, anovulatory states, early menarche and late menopause, nulliparity and unopposed exogenous estrogens. Multiparity, physically fitness and use of oral contraceptives decreases the risk to develop these cancers.[2,5,6] A continuous combined estrogen-progestagen therapy in the peri- and postmenopause possibly also reduces the risk to develop type I EC while the effects of a therapy with Tibolone on the endometrium are still controversial.[7] Type I EC develops via a characteristic sequence of hyperplastic changes of the endometrium with increasing premalignant potential.[3,4,8-11] Histologically, these estrogen-related ECs are accompanied by endometrial hyperplasia. They are well-to-intermediately differentiated, are normally diagnosed at an early stage and have an excellent prognosis. They strongly express estrogen and progestin receptors and have high response rates to progestin treatment of advanced stages.[3,4,8-13]

Type II EC has an aggressive clinical course and mostly non-endometrioid histology (usually papillary serous or clear cell) and is not associated with hyperestrogenic states.[3,8,9] It develops from the atrophic endometrium of elderly women, who do not have the classical risk factors for EC. These patients tend to be slim, are physically fit and as a rule have never used estrogen-replacement therapy. On diagnosis, type II EC is characterized by deep myometrial invasion and early lymph node or distant metastases. These cancers rarely express functional estrogen and/or progestin

Table 1. Differential aspects of type I and type II EC

Parameter	Type I EC	Type II EC
Cycle	Anovulatory	No disturbance
Fertility	Reduced	No disturbance
Age at menopause	>50 years	<50 years
Menopausal stage	Perimenopausal	Late postmenopausal
Endometrium adjacent to EC	Hyperplastic	Atrophic
Obesity	Mostly present	Mostly absent
Metabolic syndrome	Mostly present	Mostly absent
Tumor differentiation	>80% G1/G2	>60% G3 or upgraded
Histologic subtype	Endometroid carcinoma	Serous-papillary, clear-cell or adenosquamous carcinoma
Myometrial invasion	Superficial myometrial invasion	Deep myometrial invasion
Lymph space invasion	Rare	Frequent
Expression of PR	High	Low/ absent
Prognosis	favorable	poor

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Table 2. Genetic differences between type I and type II EC

Parameter	Type I EC	Type II EC
K-ras	Mutational activation	—
C-myc, c-jun		Overexpression
hTERT		Overexpression
β-catenin	Gain of function mutations	—
PTEN	Loss of function mutations	—
p53	Inactivating mutations (late event, 5-10%)	Inactivating mutations (early event, 80-90%)
BRCA	—	Mutation -> Increase of risk
MSI	Yes	Rare
EGF-R		Overexpression
HER-2/erb-B2	Overexpression (10-30%)	Overexpression (45-70%)
IGF-R		Overexpression
ER-α	Decrease of expression to higher grade	Rarely expressed

receptors and their response rates to endocrine therapies tend to be low. The only known risk factors are the age and a radiotherapy of the uterus (e.g., because of cervical cancer).[14] In type II EC, mutations are found early in the p53 gene. Overexpression of the *HER-2/erb-B2* gene is also discussed.[2] Their prognosis is poor.

The morphologic and clinical differences between type I and type II EC are paralleled by genetic distinctions and carry mutations of independent sets of genes (Table 2).[15-20]

Estrogen-Aassociated Endometrial Cancer (Type I)

The association between the endocrine milieu of estrogen predominance, resulting in hyperstimulation of the endometrium and an increased incidence of EC was first formally reported by Gusberg in 1947.[21] The normal endometrium is a hormonally responsive tissue. Estrogenic stimulation produces cellular growth and glandular proliferation, which is cyclically balanced by the maturational effects of progesterone.[22] Abnormal proliferation and neoplastic transformation is associated with chronic unopposed exposure to estrogenic stimulation. In a series of 170 patients who received no therapeutic intervention other than diagnostic curettage, Kurman et al[23] found that at least one-quarter of patients with atypical endometrial hyperplasia developed carcinoma compared with only 2% of patients with other types of hyperplasia. It is currently believed that estrogen-associated type I endometrial cancers (endometroid adenocarcinoma) progress through a premalignant stage of atypical adenomatous hyperplasia.[23] Type I EC´s are characterized by large numbers of genetic changes in which the temporal sequence of mutation and the final combination of defects differ substantially between individual cases. Common genetic changes in type I EC include, but are not limited to, microsatellite instability (MSI),[24-27] or specific mutations of PTEN,[28-33] K-ras,[25,34-38] and β-catenin genes.[39-41] Additional mutations in the *p53* tumor suppressor gene and/or loss of estrogen and/or progesterone receptor expression are typical features of a further malignant transformation to aggressive, dedifferentiated endometrioid endometrial carcinomas with poor prognosis (Fig. 1).[4,5]

Non-Estrogen-Associated Endometrial Cancer (Type II)

Women with type II EC are at high risk of relapse and metastatic disease. Type II EC is not estrogen driven and most are associated with endometrial atrophy (Fig. 2). Serous carcinoma is the most aggressive type of type II EC.[42,43] Clear cell carcinoma is another type of type II EC.[44] About 40% of type II EC are mixed, with an endometrioid component.[43] Histopathologic studies

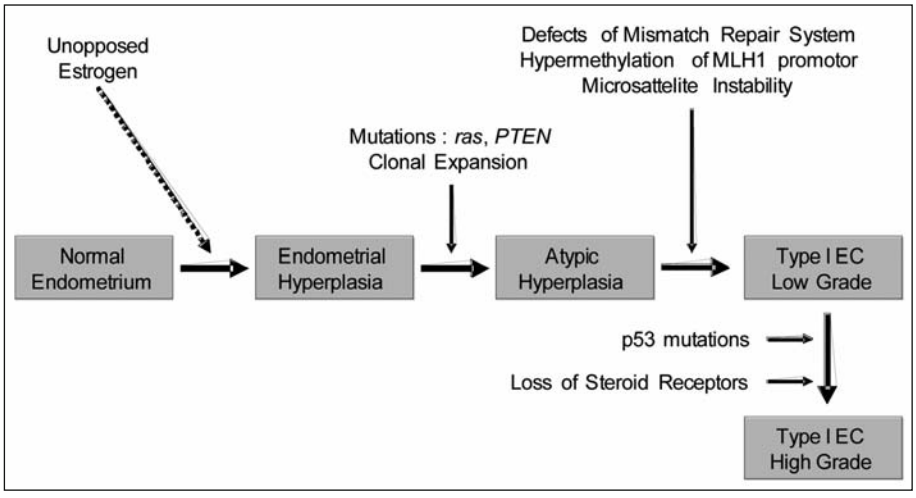

Figure 1. Carcinogenetic pathway of type I EC.

suggest that the majority of serous carcinomas develop from a distinctive lesion termed endometrial intraepithelial carcinoma (EIC), which appears to represent malignant transformation of atrophic surface endometrium.[4,45] In uteri containing serous carcinoma, the uninvolved endometrium is usually atrophic. It has been shown that when endometrial hyperplasia is identified in an uterus containing a carcinoma that is partly or exclusively serous, the hyperplasia and the carcinoma are usually topographically unrelated and appear distinct.[4] Sherman et al found that obesity and exogenous hormone use were not related to risk for serous carcinoma.[46] With advancing age, the probability of the accumulation of mutations leading to malignant transformation increases.[47]

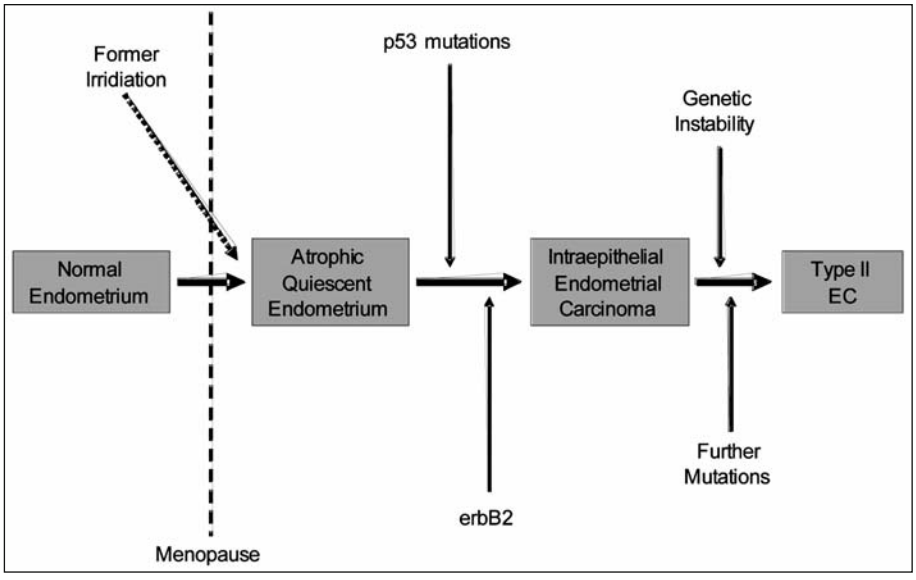

Figure 2. Carcinogenetic pathway of type II EC.

Pelvic irradiation might also add to the accumulation of mutations. The declining competence of the immune system with advancing age has been suggested as a further possible reason.[8,9,11] Mutations in the *p53* gene are well documented in type II EC and in its putative precursor EIC.[2,45] Tashiro et al found higher rates of loss of heterozygosity in serous carcinoma (100%) compared with EIC (43%) and suggested that loss of the wild-type *p53* allele can result in EIC, whereas serous carcinoma develops after the loss of the second allele.[48] Overexpression of *HER-2/erb-B2* is also discussed.[2] The timing of the appearance of *HER-2/erb-B2* mutations in the pathogenesis of type II EC is not known.

Uterine Carcinosarcomas (Malignant Mixed Müllerian Tumors)

The malignant mixed Müllerian tumor (MMMT) is a combination of carcinoma and sarcoma and is also termed uterine carcinosarcoma (UCS). MMMT's have been traditionally regarded as a subtype of type II EC. These neoplasms are rare (1-2% of all malignancies of the uterine corpus), highly aggressive and with an extremely poor prognosis. They are usually arising in elderly postmenopausal women and often presenting at an advanced stage.[49] There is an increasing evidence (clinical and molecular) suggesting that MMMT's are monoclonal malignancies, being derived from a single stem cell.[49-56] Immunological studies have suggested a common epithelial origin of MMMT's.[51] In vivo studies using nude mice have demonstrated that carcinoma cells derived from a MMMT cell line can give rise to tumors that include both epithelial and mesenchymal components whereas sarcoma cells do not.[52] In addition, the epithelial and mesenchymal components frequently share identical patterns of X-inactivation, allelic loss and p53 mutations.[53, 54] This would be highly unlikely if both components were not derived from a single stem cell. This all provides indirect evidence for the monoclonal theory of carcinogenesis in MMMT's with the carcinomatous component being the driving force and the sarcomatous component being derived from this as a result of dedifferentiation. Further molecular studies have shown that more than 25% of MMMT's have defects in their DNA mismatch repair system.[57] There is increasing evidence suggesting that MSI, a hallmark of defective DNA mismatch repair, is a common genetic change in MMMT and that defective DNA mismatch repair is a feature unique to the epithelial component of MMMT's.[58-60]

Molecular Pathogenesis of Endometrial Cancer

Oncogenes

K-ras

The *ras* (retrovirus-assiciated DNA sequences) genes are a family of proteins that have GTPase activity and are involved in signal transduction and mediate pleiotropic effects, including cell proliferation and migration. Ras genes are widely conserved among animal species. All of the genes have a similar structure and each gene encodes a 21-kDa protein. The C-terminus is necessary for full activation of downstream effectors such as Raf kinase and PI-3 kinase.[61] Point mutations in the mutational hot-spot codons 12, 13 and 61 are frequently detected in human malignancies and in different types of experimentally induced tumors in animals.[62-64] Ras mutations have been detected in different human cancers including endometrial cancer.[65,66] K-ras mutations have been identified in 19% to 46% of type I EC, but not in normal endometrium.[35,38,67-69] The frequency of K-ras mutations is higher in cancers with MSI.[69] Although both K-ras mutation and estrogen receptor (ER) are associated with type I EC, the relationship of these two factors is unclear. Tu et al could demonstrate that ER is positively regulated by Ras signaling.[70] Furthermore, the estrogen- and tamoxifen-induced transcriptional activity is enhanced by K-ras mutations.[70,71] ER seems to be one of the effectors of Ras/Raf signal transduction, involved in the tumorigenesis of type I EC.[70] Alterations of K-ras are also found in endometrial hyperplasia at a similar rate to EC suggesting that mutation in the K-ras gene is an early event in tumorigenesis of type I EC.[68] In type II EC MSI and K-ras mutations seem to be uncommon.[72-74]

C-myc and C-jun

Estrogen treatment induces immediate and transient activation of a number of nuclear oncogens in the uterus, including *c-fos*, *c-jun*, *junB*, *junD*, *N-myc* and *c-myc*.[75-78] Increased expression of these genes appears to be a direct effect of estrogen.[76] Among such estrogen-inducible oncogenes, some are considered to contribute to malignant transformation in the endometrium.[79] *C-myc* and *c-jun* are not only involved in normal growth, but may also play a role in the development of neoplasia.[79] Bai et al could demonstrate that overexpression and localization of the *c-myc* gene product may have an important role in the initiation, differentiation and progression of EC.[80] Bircan et al suggested in a study analyzing the expression of *c-myc*, *c-jun* and ER-alpha in cyclic endometrium, endometrial hyperplasia and EC that estrogen may induce *c-myc* expression leading to neoplastic transformation in human endometrium.[81] In addition, they found a positive correlation between *c-jun* expression and tumor grade in EC.[81] The association between ER and *c-jun* and hormone-mediated signaling pathways in EC seems to be different from that of normal endometrium. However, the involvement of *c-jun* in initiation, differentiation, or progression of EC is discussed controversially. *C-myc* is overexpressed in between 3% and 19% of EC. In addition, it was shown that nuclear and cytoplasmic immunohistochemical staining of *c-myc* is an independent prognostic factor in EC.[71,82,83] Neither *c-myc* nor *c-jun* seem to have specific prevalence in type I or type II EC.

hTERT

Telomerase is a unique ribonucleoprotein responsible for adding the telomeric repeats back onto the 3'-end of chromosome before each cell division and plays an important role in cellular immortalization and carcinogenesis.[84,85] Human telomerase reverse transcriptase (hTERT) is the catalytic part and therefore a key component of the telomerase.[86] In most normal somatic cell types, telomerase activity is usually undetectable but not in the endometrium.[87] This activity is dynamic throughout the menstrual cycle. It is high during the proliferative phase under influence of estrogen. In the secretory phase telomerase activity decreases under the influence of progesterone.[88] Overexpression of hTERT is involved in the development of cancer by causing telomere maintenance and potential cell immortalization.[89] Kyo et al have shown that estrogen activates telomerase through direct interaction of ligand-activated ER with the estrogen responsive element (ERE) in the hTERT 5' regulatory region of ER-positive endometrial cancer cells.[90] Other sex steroids also directly or indirectly regulate the hTERT promoter.[91,92] Wang et al demonstrated that the hTERT gene is a target of tamoxifen in a cell-specific manner.[93] Tamoxifen exerted E2 antagonistic effects on hTERT transcription in breast cancer cells but an agonistic effect in endometrial cancer cells. The authors could further show that tamoxifen activates the MAPK cascade in the endometrial cancer cells, but not in breast cancer cells. The activation of hTERT mRNA expression was effectively blocked by a MEK inhibitor, suggesting that the MAPK pathway is involved in the tamoxifen-induced activation of hTERT.[93] The effects of tamoxifen on abnormal endometrial proliferation are complex, but induction of hTERT and subsequent telomerase activation may be one component of these effects. Patients undergoing a prolonged adjuvant tamoxifen therapy against breast cancer should therefore be monitored for endometrial telomerase activity.[93] Recently Chen et al have shown that antisense oligonucleotides of hTERT effectively inhibit the growth of EC.[94] In a more recent study Zhou et al demonstrated that arsenic trioxide inhibits proliferation of EC cells through induction of apoptosis and by inhibition of telomerase activity and hTERT mRNA transcription.[95] Inhibition of telomerase activity might be a new strategy for therapy or prevention of EC. However, further studies are necessary to establish the exact role of hTERT in EC.

β-Catenin

Catenins are a group of cytosolic proteins which interact with the cytoplasmic domain of cadherins.[96,97] Cadherins are essential to the formation of cell-cell contacts and the stabilization of tissue architecture.[97] β- and γ-catenin bind to the catenin-binding domain of cadherins and mediate the binding of the complex to α-catenin.[96,97] Besides β- and γ-catenin are central players in the oncogenic Wnt signaling pathway.[98] They are downstream transcriptional activators in the Wnt signal transduction in which their activity is closely controlled by the APC tumor

suppressor gene.[99] In this context β-catenin plays an important role in oncogenesis and is implicated in the development of EC.[41] Mutations affecting the phosphorylation sites of the β-catenin gene (CTNNB1) produce constitutively stable proteins in a variety of human cancers, including type I EC.[100,101] Consequently, increased nuclear levels of β-catenin induces a higher transcriptional activation through lymphoid enhancer factor/T cell factor (LEF/TCF).[102] LEF/TCFs normally mediate Wnt signals in the nucleus by recruiting β-catenin and its co-activators to Wnt response elements (WREs) of target genes. Overactive LEF/TCFs drive the cells to transform.[103] Gain of function mutations of CTNNB1 are found in 25% to 38% of type I EC but none were observed in type II EC.[39-41,104] CTNNB1 mutations and nuclear accumulation (activation) of β-catenin have been also demonstrated in atypical hyperplasia suggesting that β-catenin abnormalities arise early in the development of type I EC.[105] Nuclear accumulation is also induced by abnormal Wnt signaling as found in some type I EC with MSI.[106]

Tumor Suppressor Genes

PTEN

The tumor suppressor gene *PTEN* (phosphatase and tensin homolog deleted on chromosome 10) codes for a phosphatase that downregulates the phosphatidyinositol 3-kinase (PI3-K)/Akt signaling pathway of growth factor receptors.[107-109] The *PTEN* gene is localized to 10q23, a chromosomal region subject to frequent loss of heterozygosity (LOH).[107] Decreased *PTEN* activity and therefore increased activation of Akt lead to increased cell proliferation and resistance to apoptosis.[110,111] Inactivation of *PTEN* is the most common genetic defect in type I EC with rates ranging from 34% to 83%.[28,32] When analyzed according to histological type, *PTEN* mutations are found almost exclusively in type I EC. In the normal endometrium no *PTEN* mutations were found. *PTEN* mutations are found at higher rates in tumors with MSI (up to 85%) and are also seen in endometrial hyperplasia with and without atypia.[30,31] *PTEN* mutations occur at the earliest detectable stage of endometrial carcinogenesis.[112] The *PTEN* defect observed most frequently is an inactivation of both alleles resulting in a complete loss of function. Even a hemizygous inactivation leading to a protein deficient state seems to be functionally significant when combined with defects of other genes within this pathway. Oda et al demonstrated that the PI3K/Akt pathway is extensively activated in EC and that a combination of defects in the catalytic subunit alpha of PI3K (PIK3CA) and *PTEN* plays an important role in the development of these tumors.[113,114] The tumor suppressor gene *PTEN* is also involved in the regulation of telomerase activity by inhibition of Akt activation and a subsequent decrease of hTERT expression. Loss of *PTEN* may therefore allow endometrial cells to express high levels of telomerase activity, facilitating neoplastic transformation.[115] Highly mitotic cells, such as normal estrogen-stimulated proliferative endometrial glands, contain abundant *PTEN* protein. Suppression of *PTEN* expression in a mitotically active estrogenic environment (unopposed by progestins) may compromise growth control more than loss of *PTEN* protein in mitotically quiescent cells. Individual *PTEN*-negative glands in estrogen-exposed endometria represent the earliest recognizable stage of endometrial carcinogenesis, which is followed by proliferation into dense clusters that form discrete premalignant lesions.[5,28]

p53

The *p53* tumor suppressor gene is located on chromosome 17 and encodes a 53 kDa nuclear phosphoprotein that induces proliferative arrest or apoptosis through induction of $p21^{Waf1/Cip1}$ and hMdm2 to prevent propagation of cells with damaged DNA.[116] Mutations in *p53* can introduce stop codons resulting in a truncated, nonfunctional protein. Since these truncations often involve the C-terminus, hMdm2 cannot bind to the *p53* protein (TP53) and therefore nonfunctional TP53 accumulates in the cell. Almost 80% of *p53* mutations are missense mutations leading to synthesis of a TP53, lacking its specific DNA binding function and accumulation in the nucleus.[117,118] In addition, missense mutations in *p53* often affect amino acids involved in post-translational modifications affecting the stability of TP53.[119] *p53* protein overexpression in EC is associated with high grade tumors, lymph node metastasis and myometrial invasion.[67] In type I EC, TP53

overexpression is frequently observed, however, *p53* mutations are rare and, if present, not related to TP53 overexpression.[67,120] Most type I EC that harbor *p53* mutations are large high-grade tumors, which suggests that *p53* mutations in type I EC are more closely related with dedifferentiation, as in the case of other tumor systems.[4,67] Aberrant accumulation of inactivated TP53 is found in approximately 5% of type I EC.[67] A high level of inactivated TP53 is also an independent prognostic factor.[121] Pijnenborg et al demonstrated that TP53 overexpression is predictive for recurrent type I EC and mostly not correlated with *p53* mutations.[122] Concomitant low expression of hMdm2 and $p21^{Waf1/Cip1}$ in tumors with TP53 overexpression suggests a dysfunction in this signal transduction pathway.[122] In type II EC, TP53 overexpression is also frequently present but associated with truncating *p53* mutations.[48] *p53* mutations are found in 71% to 85% of the type II EC and in contrast to type I EC are early events in the development of type II EC.[123-125]

BRCA

Germline *BRCA* gene mutation carriers are found to have an increased risk of developing breast or ovarian cancer and to a lesser degree, colon cancer. Male *BRCA* mutation carriers are also inclined to an increased risk of breast, colon, or prostate cancer.[126,127] Following the paradigm of tumor suppressor genes, one mutated allele of *BRCA1* or *BRCA2* is inherited and then somatic mutation occurs to alter the second allele, such that tumors invariably contain two mutant alleles. There are limited data regarding whether or not *BRCA* mutation carriers are also at increased risk for EC. Thompson and Easton have recently reported that *BRCA1* mutation carriers have a 2.7-fold increased risk to develop EC.[128] Other studies suggest that *BRCA* mutation carriers have an increased risk of type II EC.[129,130] Other groups did not find any correlation.[131,132] In a prospective study Beiner et al did not find that *BRCA* mutations directly increase the risk of EC.[133] They suggested that the main contributor to the increased risk of EC among these women was tamoxifen treatment of previous breast cancer or the preventive use of tamoxifen.[133] Hornreich et al observed two sisters with advanced serous papillary carcinomas of endometrial and ovarian origin, carrying the same *BRCA1* mutation.[134] LOH analysis of the EC showed loss of the wild-type allele, suggesting a causal relationship between the germline *BRCA1* mutation and development of type II EC.[134] However, whether or not germline *BRCA* mutations play a role in the development of EC remains unclear.

DNA-Mismatch Repair Genes

Type I ECs are characterized by defects in DNA mismatch repair, as evidenced by the microsatellite instability (MSI) or replication error repair (RER) phenotype. Microsatellites are short segments of repetitive DNA bases that are scattered throughout the genome and found predominantly in noncoding DNA. MSI is the property to develop changes in the number of repeat elements as compared with normal tissue due to DNA repair errors made during replication. MSI is found in 17 to 25% of sporadic type I EC but is rarely (<5%) present in type II EC.[29,72,135] MSI was detected in atypical hyperplasia associated with carcinoma but not in atypical hyperplasia without associated carcinoma, suggesting that mismatch repair defects may occur in the transition between the two lesion.[4,24] Somatic mutational inactivation of known mismatch repair genes does not account for the great majority of sporadic ECs with MSI. Instead, mismatch repair genes (i.e., MLH-1) are inactivated or silenced by gene promoter hypermethylation (epigenetic effect).[136] This mechanism is not found in type II EC.[136]

Growth Factor Receptors

EGF Receptor

The role of epidermal growth factor receptor (EGF-R) in endometrial cancer is still disputable. The EGF-signaling pathways involve four known receptors (EGF-R, erbB2/HER-2/neu, erbB3 and erbB4) and various ligands, like e.g., epidermal growth factor (EGF), amphiregulin and transforming growth factor-alpha (TGF-α).[137] The members of the erb-B family belong to transmembrane receptor tyrosine kinases and activation of these receptors generally requires

tyrosine phosphorylation of the cytoplasmatic tyrosine kinase domain.[138,139] Most tyrosine kinase receptors are activated by ligand-induced dimerization. EGF and TGF-α stimulate homodimerization of the EGF receptor, but, under certain conditions, heterodimerization with other family members like HER-2 also occurs. Activation of the EGF-R by its ligands induces activation of *ras* and phosphorylates further downstream substrates of the mitogen activated protein-kinase (MAP-kinase) family including extracellular signal-regulated kinases (ERK-1/2), *c-jun* N-terminal kinase (JNK) and MAP-kinase p38 and activates EREs.[137] EGF-R is expressed at comparable levels in normal and hyperplastic endometrium and may be overexpressed in invasive EC.[140] Niikura et al, however, described in advanced disease increased co-expression of EGF-R and TGF-α.[140] Overexpression of TGF-α was described in poorly differentiated EC and negatively correlates with ER expression.[140-142] Jasonni et al found low levels of EGF-R expression in type I EC and high levels in EC with benign squamous metaplasia, whereas in mucinous and serous EC EGF-R and TGF-α expression was not found.[143,144] In contrast, overexpression of EGF-R was found to be strongly correlated with tumor metastases and survival in patients with EC, independent of the histologic type.[145,146] In a more recent publication EGF-R expression was described not to be increased in endometrioid EC compared to normal endometrium, but the authors found an increased expression of HER-4 and the EGF-R ligands TGF-α and heparin-binding epidermal growth factor-like growth factor (HB-EGF).[147] EGF-R expression was also described in the majority of endometrial carcinosarcomas. Interestingly EGF-R was predominantly overexpressed in the sarcomatous components of the tumors, whereas HER-2 was predominantly overexpressed in the carcinomatous components.[148] Taken together, EGF-R expression and expression of its ligands TGF-α and HB-EGF correlate with occurrence of myometrial invasion and/or metastases and poor prognosis in patients with EC. Negative correlation of ER expression and TGF-α expression in advanced disease indicates a conversion of formerly ER dependent growth to predominantly EGF-R mediated autocrine growth-regulation by alternative ligands like TGF-α and HB-EGF. Smith et al found a strong correlation of G-protein coupled receptor 30 (GPR30), a 7-transmembrane receptor for estrogen and EGF-R expression in patients with advanced EC, high grade and biologically aggressive histologic subtypes.[149] GPR30 represents an alternative cytoplasmic estrogen-responsive receptor that is overexpressed in tumors where estrogen and progesterone receptors are down-regulated and in high-risk EC patients with lower survival rates. Activation of GPR30 by estradiol induces metalloproteinase activity, release of growth factors like HB-EGF by tumor cells and trans-activation of the EGF-R.[150] In vitro experiments with specific EGF-R tyrosine kinase inhibitor gefitinib showed equal inhibition of EGF-R autophosphorylation and MAP-kinase activity in cells representing type I and II EC. In cells representing type II EC high basal phosphorylation of numerous signaling molecules that were not inhibited by gefitinib indicated, that other growth factor pathways like PI3K/Akt/PKB signaling are active in addition to EGF-R.[151,152] Further investigations to understand cross-talk mechanisms of the EGF-R and its potential role in targeted therapy of EC are necessary.

HER-2/erb-B2

The *HER-2/erb-B2/neu* gene encodes a 185-kDa transmembrane receptor tyrosine kinase of the EGF-R/erb-B family. HER-2 functions as a preferred partner for heterodimerization with members of the erb-B family and induces ligand independent autosignaling via specific tyrosine kinase phosphorylation.[153] HER-2 overexpression was described in about 10-30% of type I EC and in 45-70% of type II EC, respectively.[83,154-157] However, more recent studies of large series of serous carcinomas found that only 18-43% of the tumors overexpressed HER-2.[158,159] EGF-R and HER-2 co-expression is inversely correlated with grade of differentiation and with ER and PR content and predicted a poor prognosis in patients with EC.[160] HER-2 overexpression and gene amplification correlate inversely with disease specific survival and progression-free survival in patients with EC.[159,161] In a retrospective analysis Saffari et al could show that among patients with HER-2 overexpression of EC, adjuvant chemotherapy or radiation therapy after surgery were associated with an improved overall survival.[162] HER-2 overexpression negatively correlates with expression of ER and PR and suggests the developmend of hormone-independent growth in a

subgroup of EC patients.[160,163,164] Cross-talk mechanisms of HER-2 with other signal pathways (like PI3K/pAkt/PKB pathway) are comparable to those of the EGF-R. On the other hand, HER-2 associated tyrosine phosphorylation acts by ligand-independent autosignaling via HER-2/HER-X heterodimerization.[153] The extracellular domain of the HER-2 oncogene product p185 provides an attractive therapeutic target for treatment with the monoclonal antibody trastuzumab. In preclinical studies trastuzumab showed antiproliferative activity in ER positive and ER negative endometrial cancer cells.[165,166] Treeck et al could show, though, that in endometrial cancer cells HER-2 signaling was inhibited by trastuzumab only in the absence of estradiol. In these cells estradiol counteracted the inhibitory effects of trastuzumab by rapid phosphorylation of ERK-1/2, probably triggered by GPR30 and inhibitory effects of trastuzumab were restored by cotreatment with pure antiestrogen fulvestrant.[167] These findings suggest that there is intensive cross-talk between hormone-dependent growth regulation and signal transduction of members of the erbB family leading to rapid resistance of single agent targeted therapies. Recently, trastuzumab showed encouraging activity in a few patients with HER-2 overexpressing advanced EC.[168,169] Clinical trials to evaluate efficacy of trastuzumab with or without antiestrogen or chemotherapy combinations in patients with HER-2 overexpressing EC are currently ongoing.

IGF Receptor

The type I insulin-like growth factor receptor (IGF-R) is a transmembrane receptor tyrosine kinase composed of two α subunits and two β subunits.[170] The activation of IGF-R requires binding to either of its ligands, IGF-I or IGF-II. As a result of ligand-dependent IGF-R activation via intracellular tyrosine phosphorylation of the β subunits multiple downstream signaling pathways are activated, including the MAP-kinase pathway and the phosphatidylinositol 3-kinase (PI3K). The latter activates Akt/protein kinase B and induces proliferation.[171,172] PTEN negatively regulates PI3K activity by dephosphorylation of phosphoinositol triphosphate (PIP-3).[111] Lower levels of phosphatase activity like loss of PTEN expression, leads to hyperactivation of the PI3K/pAkt pathway. IGF-R is expressed mainly in endometrial epithelial cells, its ligands IGF-I and IGF-II are expressed in endometrial stromal cells and their expression is associated with endometrial differentiation.[173,174] Estrogen-dependent activation of ER-α can up-regulate the expression of IGF-R.[175] McCampbell et al found increased IGF-R expression in biopsies from complex atypical hyperplasia and activated downstream components like increased pAkt levels independent of PTEN expression.[176] Specific binding sites for IGF-I were increased in endometrial cancer and IGF-R overexpression was found in 67% of endometrial cancers, independent of histologic type.[177-179] The role of autocrine IGF-R mediated growth regulation in endometrial cancer is still under discussion. In EC cells in vitro autocrine growth regulation was shown to be mediated by TGF-α and IGF, but not by EGF.[180] About 95% of IGF-I and IGF-II is associated with membrane-bound IGF binding proteins (IGFBP). Kleinman et al could show in endometrial cancer cells that IGF-R dependent stimulation of cell growth depends on IGF levels as well as levels of IGFBP subtypes. In these cells IGFBP levels were decreased and IGF-R levels increased by estradiol or tamoxifen stimulation.[181,182] These findings were underlined by various serum levels in EC patients showing decreased levels of IGFBP subtypes and increased IGF-1 levels.[183-187] Of note, obesity and diabetes mellitus are accepted risk factors for EC. It has been discussed whether increased insulin levels are associated with development of EC. High affinity binding-sites for insulin were demonstrated in EC cells and insulin stimulated cell growth.[188] However, clinical evaluations of C-peptide levels showed modest support to the hypothesis that hyperinsulinaemia is a risk factor for endometrial cancer.[189]

Angiogenic Factors

Angiogenesis is a multistep process essential for tumor growth, invasion and metastatic spread.[190] Microvessel density has been widely used as a measure of tumor-associated angiogenesis. Various studies have shown that high intratumor microvessel density in EC is associated with advanced clinical stage, increased risk of recurrent disease and poor prognosis.[191] In stage I endometrial carcinoma, greater depth of invasion and higher tumor grade are directly correlated with angiogenic

intensity.[192] Vascular endothelial growth factor (VEGF) is the major stimulus for endothelial cell proliferation in EC and is, therefore, associated with high angiogenesis.[193] VEGF is an independent predictor of poor prognosis, particularly within stage I endometrial disease.[194] However, VEGF expression did not correlate with histological grade or the number of microvessels in the tumor area. Since the stimulating effect of VEGF on endothelial cells is basically dependent on the presence of VEGF receptors, i.e., flk-1, the detection of a functionally intact angiogenic pathway VEGF/flk-1 is a more reliable and independent prognostic parameter.[195] The expression of another angiogenic factor, thymidine phosphorylase (TP), correlates with increased microvessel density in EC.[196] TP expression is related to the adverse histopathological variables of the type II EC, such as high tumor grade, deep myometrial invasion and advanced stage of disease.[195] Stefansson et al have recently examined the significance of vascular proliferation and the degree of pericyte coverage in a large and population-based series of EC with complete follow-up.[197] They found that vascular proliferation is the strongest angiogenic marker independent of other prognostic factors. Decreased pericyte coverage was significantly associated with vascular invasion by tumor cells and reduced patient survival.[197] Additionally, in the same study peritumoral lymphatic vessel density was shown to contribute to the clinical progress of EC.[197]

Hormone Receptors and Aromatase

Estrogen Receptor

The steroid receptors for estrogen (ER) are composed of six functional domains. The DNA-binding domain (DBD) is relatively conserved and targets the receptors to the estrogen responsive elements (EREs). The E region of the steroid receptors contains a multifunctional domain and is involved in ligand-binding, receptor dimerization, nuclear localization, nuclear coactivator/corepressor interaction and ligand-dependent activating function.[198] The two main isoforms of the ER, ER-α and ER-β, show structural differences resulting in distinct ligand affinities and physiologic properties. For example, tamoxifen exhibits partial agonist activities after binding to ER-α whereas it acts mainly as pure antagonist when bound to ER-β.[199] ER-α is the predominant ER isoform in endometrium.[200] Both isoforms are capable of forming ER-α/ER-β heterodimers and thus influence each other function.[201,202] In this context, ER-β has been shown to function as a dominant inhibitor of ER-α.[203] In addition, both ER-α and ER-β are represented by several isoforms resulting from alternative splicing and these splice variants can exhibit altered hormone-binding effects on EREs and/or transcriptional properties.[204-206] Beside the described classic genomic activation of ER-α and ER-β, both receptors have been shown to regulate transcription by nonclassic genomic activation of components of the activating protein-1 (AP-1) pathway.[207] The nongenomic mechanism of ER action is cross-talk with the signal-transduction of growth-factor receptor cascades, for example via activation of MAP-kinase (ERK-1/2) and/or the PI3K/pAkt pathway.[208,209] One possible critical step in estrogen-dependent tumorigenesis might be an imbalance in ER-α and ER-β expression. Expression of ER-α decreases from hyperplastic and grade 1 endometrioid EC to grade 3 tumors. ER-α is rarely expressed in type 2 EC.[200,210,211] Expression levels of ER-β are low in normal endometrium and do not alter during tumor differentiation, suggesting a shift to decreased ER-α/ER-β ratio.[212,213] Transcriptional splicing errors for ER-α and ER-β have been described for EC, potentially leading to uncontrolled proliferation. Although there is no homogenous pattern in the development of EC for the described splice variants, some of them are found at increased levels in EC.[214-218] Recent investigations evaluated expression of steroid receptor cofactors 1-3 (SRC) in EC. Balmer et al found increased expression of SCR3 member AIB1 (amplified in breast cancer-1) in hyperplastic endometrium and in EC. Expression of AIB1 correlated with higher grade of carcinomas, potentially augmenting ER action in these tumors.[219] Kershah et al found increased levels of mRNA of SRC-1-3 in EC samples, whereas Uchikawa showed decreased levels of SCR-1 in EC topographically correlated with decreased ER expression, indicating sex steroid independent growth in these tumors.[220,221] ER activation can also be mediated in a ligand-independent way. For example, PTEN loss in endometrium activates Akt and

results in increased phosphorylation of ER-α. ER-α phosphorylation even in the absence of ligand results in activation of EREs and transcription.[222] Estrogen-dependent growth in EC might also be mediated through G-protein coupled GPR30, inducing MAP-kinase and Akt activation.[150,223] Overexpression of GPR30 was shown in EC with down-regulated expression of ER-α/ER-β and PR and overexpression correlated with higher grade and lower survival.[149] The mechanisms of estrogen-dependent growth and potential antiestrogenic therapeutic strategies in EC are complex and require more global understanding of cross-talk action patterns between ER and its SRCs, the alternative estrogen receptor GPR30 and the signal-transduction of growth factor receptors to define subgroups of estrogen-dependent EC.

Progesterone Receptor

The steroid receptors for progesterone (PR) exist in two isoforms, PRA and PRB. These two receptors are almost identical, except that PRB contains a third transcription-activating functional domain, AF-3.[224,225] PRA has been shown to act in a dominant negative fashion and antagonizes the transcriptional activity of PRB and the ERs.[226] On simple progestin-responsive elements (PREs) PRA and PRB display similar transactivational activity, but PRA's transcriptional activity is more complex and cell and response element specific.[227] Loss of the inhibitory effects of PRA and disruption of the PRA/PRB ratio is thought to be involved in estrogen-induced endometrial hyperplasia and EC.[228-231] One factor for the disruption of the PRA/PRB ratio might be receptor gene polymorphism.[232] Low PR expression was shown to be associated with increased risk for tumor relapse, but in patients showing PR expression and PR gene polymorphism the risk was even higher.[233] Regarding the prognostic value of both PRs, only decrease of PRB expression seems to reflect poor prognosis in patients with EC.[234,235] PRB expression is found to be distributed in the cytoplasm in EC tissues, whereas PRA expression is only found in the nuclei, suggesting nongenomic actions of PRB.[236] Transfection of PRB and treatment with progestins in human endometrial cancer cells resulted in growth inhibition, inhibition of cyclin D1 expression, down-regulation of metalloproteases and down-regulation of cellular adhesion molecules.[237,238] PRB-expression is inversely correlated with p53 gene mutation and tumor grading.[235] Serial biopsies of patients with advanced type 1 EC treated with medroxyprogesterone showed no increased apoptosis but down-regulation of Ki-67 expression. Decreased Ki-67 expression was only observed in grade 1 and 2 tumors with high PR expression.[239] In EC cells ligand-bound PRB can inhibit the transcriptional activity of members of the AP-1 family and in particular, *c-jun*. Thus, progesterone might antagonize stimulatory effects of estrogens on AP-1.[240] In addition, ligand-bound PRB can inhibit NFκB activity through transcriptional control in EC cells.[241] Progestins are currently leading standard in the treatment of advanced type 1 EC. The PR isoforms, PRA and PRB, play important roles in growth control of EC and offer targets for novel therapeutic strategies. However, to understand the mechanisms of action of PRA and PRB in EC, especially regarding differences between type 1 and 2 EC, further evaluations are required.

Aromatase

There is no consistent evidence of increased concentrations of circulating endogenous estrogen in women with EC, but local concentration of estradiol in EC tissues was reported to be higher than that in blood and in normal endometrium.[46,242-246] These data suggest that endometrial cancer itself synthesizes estradiol as part of positive autocrine growth-regulation. CYP19 (aromatase) gene polymorphism has been discussed as potential risk factor in patients with EC. CYP19 genotypes containing the longest alleles A6 and A7 (A6A7/A6A6) were found to be over-represented in patients with EC and intratumoral aromatase activity was increased especially in patients with type II EC.[247-249] Aromatase expression could be demonstrated in more than 65% of EC tissues by PCR and IHC and tumor aromatase expression did not correlate with ER/PR expression or prognosis.[250-252] Aromatase in stromal but not epithelial cells correlated positively with advanced surgical stage and poor survival.[253] In addition, aromatase expression was also demonstrated in low-grade endometrial stromal sarcomas.[254] Interestingly, very high intratumoral aromatase activity could be described preferably in poorly differentiated endometrioid carcinomas and in type II EC tissues, whereas negative

aromatase activity could only be demonstrated in cases of low-risk type I EC.[255-257] Thus, although type II EC is considered as hormone-independent, increased ability of this tumor type to estrogen biosynthesis through cancer cell aromatase activity may lead to the reconsideration of such conclusion and warrants further investigation. Aromatase inhibitors showed moderate antiproliferative activity on endometrial cancer cells in vitro.[258,259] Safety data from the ATAC trial of postmenopausal women with breast cancer treated with aromatase inhibitor anastrozole indicated a preventive role of aromatase inhibitors by reducing the risk of EC.[260] A few case control studies and two phase II trials showed moderate activity of aromatase inhibitors in patients with advanced endometrial cancers.[256,261,262] Berstein et al treated 23 patients 2 weeks with aromatase inhibitors in the neoadjuvant setting and found in serial biopsies down-regulated PR expression, which was more pronounced in type II EC patients.[256] Burnett et al treated two obese premenopausal women with histologically confirmed grade 1 EC with a medroxyprogesterone/anastrozole combination up to six months leading to complete remission.[263] Although response rates in the phase II trials were low, aromatase inhibitors in the treatment of subgroups of patients, probably especially in patients with type II EC, might be useful. To define potential subgroups predictive factors for response, for example the role of intratumoral aromatase activity, are required.

GnRH Receptor

A series of papers from different laboratories has demonstrated the expression of gonadotropin-releasing hormone (GnRH, GnRH-I) in almost 100% of ECs and the expression of the GnRH receptor (GnRH-R, GnRH-I-R) in about 80% of ECs.[264, 265] Recently, the expression of a second human GnRH (GnRH-II) was reported.[266] The existence of a functional active type II GnRH receptor (GnRH-II-R) in the human being is under discussion, but there is an increasing evidence that a functionally active GnRH-II-R exists in human EC.[265, 267-270] In EC, GnRH-I, GnRH-II and their receptors are parts of a negative autocrine regulatory system of cell proliferation.[264, 267] Agonists of GnRH-I and GnRH-II inhibit the mitogenic signal transduction of growth factor receptors and related oncogene products associated with tyrosine kinase activity via activation of a phosphotyrosine phosphatase resulting in down-regulation of cancer cell proliferation.[264, 267] Induction of apoptosis is not involved. The situation is different with GnRH-II antagonists. Treatment of human EC cells with GnRH-II antagonists induces apoptotic cell death via dose-dependent activation of caspase-3.[271] The fact that treatment with GnRH-II antagonists resulted in an increase of caspase-3 activity and a loss of mitochondrial membrane potential in cultured endometrial cancer cells suggests that GnRH-II antagonists induce apoptosis in these cells at least in part through activation of the intrinsic apoptotic pathway. The antitumor effects of the GnRH-II antagonists could be confirmed in nude mice. GnRH-II antagonists inhibited the growth of xenotransplants of human EC in nude mice significantly, without any apparent side effects.[271] Thus, GnRH-II antagonists seem to be suitable drugs for an efficacious and less toxic endocrine therapy for EC.

Future Perspective

Despite the great effort made to unravel the molecular alterations associated with endometrial cancer, tumors lacking MSI phenotype or mutations in any of the studied genes suggest the existence of unrecognized pathways in the development of EC. Hopefully, ongoing and future research will help to understand better the mechanisms leading to the formation of these cancers. New technologies such as the cDNA microarray technology for identifying differences in gene expression patterns in individual ECs will make more clear a distinctions in the biology and clinical outcome of these neoplasms. The increased knowledge of the molecular pathology of the individual EC will assist to develop techniques to identify premalignant diseases, improve disease management and treatment and invent specific target therapies based on molecular pathways.

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