Gatekeeper for Endometrium: the PTEN Tumor Suppressor Gene

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The complexity of genetic alterations in invasive cancers and the heterogeneity of tumor cell populations hamper attempts to translate molecular understanding at the genetic level into accurate diagnostic and therapeutic approaches. Delineation of molecular changes in the initial stages of tumor development is, therefore, highly desirable because such information can be translated into more effective cancer prevention and treatment strategies. Significant advances have been made in understanding the molecular events that occur as normal tissues evolve—often into precancerous lesions, some of which eventually progress to cancer. In some cancers, such as colorectal carcinomas and gliomas, details of distinct molecular pathways have been identified. In most cancers, however, no consistent pattern of genetic alteration is convincingly linked to the initiation or progression of the disease.

In the case of endometrial cancer, molecular details are beginning to emerge that may eventually help advance our understanding of the complex histopathology of this disease. Two major pathogenetic variants of endometrial carcinoma, endometrioid and serous, seem to evolve via divergent pathways and contain distinct genetic abnormalities. Serous endometrial carcinoma, the less common variant, is highly aggressive and estrogen independent. More than 90% of serous tumors contain p53 mutations (1).

The estrogen-related endometrioid adenocarcinomas account for up to 80% of the endometrial cancer cases and appear to arise via a progression pathway. Frequently, the advanced carcinomas are temporally and spatially associated with endometrial hyperplasia, which constitutes a range of heterogeneous precancerous lesions. Complex atypical hyperplasia (CAH), the most advanced component of this histopathologic spectrum, is believed to be the direct precursor lesion of endometrioid carcinoma. Subsets of endometrioid carcinoma were found to contain K-ras (also known as KRAS) mutations (15%–20%) (2) and the microsatellite instability (MI) phenotype (20%–30%) (3), which is indicative of DNA mismatch-repair defects. Both of these abnormalities were also detected in CAH.

In 1997, several groups (4–6) reported mutational inactivation of the tumor suppressor gene PTEN in 33%–55% of low-grade as well as in high-grade endometrial cancers of endometrioid histology. More importantly, two independent studies (7,8) described mutations in the PTEN gene in about 20%–30% of CAH, the putative precursor lesion of endometrioid carcinoma. Their observations strongly suggest the involvement of the gene in the initial stages of tumor development. A comparative analysis of the CAH lesions with and without synchronous carcinomas provided evidence that mutation of the PTEN gene is an early event and may precede the development of the MI phenotype (8).

In this issue of the Journal, Mutter et al. (9) report a much higher frequency of mutations in both adenocarcinomas (83%) and endometrial hyperplasias (55%). As Mutter et al. suggested, this high frequency may be due to a combination of preselection bias for the biopsy specimens of endometrioid histology by computerized morphometric imaging analysis and the denaturing gradient gel electrophoresis technique used for mutation detection. Homozygous inactivation of the gene occurred in 33% of the tumors, whereas 50% of the tumors contained monoallelic mutations. Furthermore, by use of immunohistochemistry (albeit on a different set of biopsy specimens), the authors detected loss of expression or decreased expression of PTEN in most, if not all, cancers and precancers and in a group of poorly classified lesions that are intermediate between normal epithelium and precancer. In the future, quantitative analysis of PTEN expression and its association with the genotype in the same tumor biopsy specimens would help clarify whether hemizygous inactivation of the gene in endometrioid carcinomas and precancerous lesions relates to the partial or total loss of its expression. One PTEN transgenic study (10) revealed that PTEN haploinsufficiency in mice generates hyperplastic foci in the endometrium that closely resemble the histopathologic spectrum of human endometrial precancers.

Mutter et al. (9) also explored the possible association between the widely accepted endocrine risk for endometrial carcinoma and PTEN expression. They reported loss of expression of PTEN protein in the estrogen-exposed endometrial epithelium. In two of the seven tissue samples examined, PTEN-negative glands were interspersed among PTEN-positive areas; in contrast, contiguous groups of PTEN-negative glands were observed in both cancersous and precancerous lesions.

Exposure to estrogen unopposed by the differentiating effect of progesterin is considered a risk factor for the development of endometrial hyperplasia and carcinoma. The molecular basis of this observation is not known, but it likely involves interaction between the hormone and specific gene(s). The scattered loss of PTEN expression in unopposed estrogen-exposed endometrium, if borne out by future molecular studies on an expanded set of samples, would elucidate one such interaction at the earliest stage of transition of the normal endometrial epithelium to a precancerous state. Also, it would provide an exciting challenge to decipher the molecular details of interactions between genetic and hormonal events in an epithelium that is subjected to orderly cyclic proliferation and regression under the influence of hormones. In this context, it is noteworthy that serous tumors that arise via a different genetic pathway are hormone independent and do not harbor PTEN mutations. It is possible that the two histologic variants arise from two different endometrial stem cells. Information on the transcriptional regulation of the PTEN gene would provide insight about its role (or the lack of one) in the evolution of endometrial cancers arising from two distinct genetic pathways.

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Structural and functional analyses of PTEN protein suggest that it is multifunctional. Reconstitution experiments have shown that, depending on the cellular context, growth suppression by PTEN may be mediated by different mechanisms. In endometrial cancer cell lines and in other types of carcinoma cell lines, introduction of the PTEN gene results in induction of apoptosis (11); in contrast, in glioblastoma cell lines, cell cycle progression is blocked at the G1 phase by elevated levels of the cell cycle inhibitor p27 (12). On the basis of the presence of the protein phosphatase signature motif in its amino-terminal domain, PTEN was originally considered to be a dual specificity phosphatase (13). However, its principal physiologic activity has now been shown to be dephosphorylation of the lipid second messenger phosphatidylinositol 3,4,5-triphosphate (PIP3) (14). The recently described crystal structure of PTEN (15) revealed an active-site pocket that is surrounded by basic residues and much wider than those of protein phosphatases and can accommodate the bulky size of the acidic PIP3 substrate. Other notable features of PTEN’s structure that are relevant to its physiologic activities are the carboxy-terminal C2 domain that is important for membrane association and the PDZ-binding motif that is involved in protein–protein interactions that mediate the assembly of membrane-associated multiprotein signaling complexes (16,17). By virtue of its membrane association and ability to modulate the levels of PIP3—thus counteracting the survival factor gene Akt/PKB—PTEN is centrally placed to regulate a network of overlapping signaling pathways that affect cell proliferation, migration, differentiation, and death.

Inactivation of the PTEN gene occurs at different stages of tumor development and may serve different functions, depending on the cell type. An abnormal “landscaper” function (Fig. 1) that results in the development of hamartomas and subsequent tumors was attributed to inherited PTEN mutations (18). Loss of PTEN expression in the vast majority of endometrioid carcinomas and in precancerous lesions, probably in the earliest stages of tumor development as shown by Mutter et al. (9), suggests a “gatekeeper” role (19) for the PTEN gene in the endometrium. This gatekeeping function of the PTEN gene appears to be selective for the endometrioid cell lineage that proliferates in a hormone-rich environment. Germline mutations in the PTEN gene occur in Cowden syndrome, of which endometrial cancer is a minor component. Endometrial carcinoma is the second most frequent cancer in the hereditary nonpolyposis colorectal carcinoma (HNPCC) (20) that has germline mutations in DNA repair enzymes with a “caretaker” function (19). It can also be found in Li–Fraumeni syndrome and in familial breast–ovarian cancer. However, there are no typical hereditary endometrial cancers. Thus, unlike other gatekeeper tumor suppressor genes, such as Rb in retina, APC in colon, VHL in kidney, and PTC in skin, which are inactivated in both inherited and sporadic forms of cancers, inactivation of the PTEN gene occurs only in sporadic endometrial carcinoma. It would be interesting to know if endometrial carcinomas arising in HNPCC families, as well as in families in which clustering of endometrial cancer was reported in two or more generations (21), have PTEN inactivation.

In contrast to its involvement in the earliest stage of endometrial carcinoma, loss of PTEN expression is associated with high Gleason score and advanced pathologic stage in prostate cancer (22). Also, PTEN mutations occur predominantly in aggressive primary glioblastomas that evolve de novo (23). In such tumors, where mutational inactivation of PTEN is a consistent feature of advanced disease, loss of PTEN perhaps facilitates the emergence of the aggressive phenotype.

PTEN is a close second to p53 in terms of its mutation frequency (24) and probably rivals p53 in its ability to regulate multiple signal transduction pathways that affect diverse and vital cellular functions. Whether the wild-type PTEN gene functions as a gatekeeper or whether its loss provides a landscaper or facilitator role depends on the cellular context. By virtue of its ability to modulate fundamental cellular processes, PTEN is indeed well suited to play these multiple roles in many different cell types. Elucidation of the molecular details of PTEN’s diverse activities, especially in the cell type(s) where it functions as a gatekeeper, should suggest molecular targets for the development of effective prevention and treatment strategies.

![Fig. 1. Potential roles of PTEN in human cancers. WT = wild-type.](image-url)

The landscaper role for PTEN was originally proposed for hamartomaticous polyps with inherited PTEN mutations (19). The proliferating stromal cell population is thought to provide a favorable landscape for the evolution of epithelial tumors. This attractive idea needs clarification of inactivation of WT PTEN allele in stromal and/or epithelial cell types of hamartomas.

The PTEN gene appears to be the gatekeeper (19) for endometrium. PTEN mutations in precursor lesions of endometrioid cancer and loss of PTEN expression in scattered groups of cells of estrogen-exposed endometrial epithelium indicate that PTEN inactivation is the key initiation event in endometrioid tumorgenesis. Consequently, there is deregulation of cell growth and/or apoptosis.

Most low-grade tumors require additional genetic mutations that facilitate progression to aggressive phenotype and acquisition of metastatic potential. For example, in the absence of these additional genetic alterations, low-grade astrocytomas may exhibit slow progression and may not progress to glioblastoma (25). PTEN mutations occur in subsets of advanced stages of prostate carcinomas and in primary glioblastomas. Although the initiation and progression phases of rapidly evolving primary glioblastomas are not known, it is likely that mutated PTEN, along with other genetic alterations, facilitates the emergence of this malignant tumor.
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