The Biology Behind

The Expanding Role of PTEN in Neoplasia: A Molecule for All Seasons?¹


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Abstract
Not since the discovery of p53 has another molecule received as much attention as PTEN. In the 5 years since the discovery of PTEN, encoding a dual specificity phosphatase tumor suppressor on 10q23, it has been shown to be a susceptibility gene for an inherited cancer syndrome, Cowden syndrome, and for several developmental disorders; it has been shown to play a prominent role in normal murine and human development; and it has been shown to be instrumental in cell cycle arrest, apoptosis, and/or possibly cell migration and cytoskeletal affairs. Initial work on cancer cell lines had suggested that PTEN caused every type of cancer because it was reported that a relatively high frequency of a variety of cancer cell lines, whether derived from solid tumors or hematological malignancies, had homozgyous or compound heterozygous genetic alterations involving PTEN. Such data, together with the germ-line human and murine model data, suggested that PTEN mutations occurred “early” in sporadic tumorigenesis. However, subsequent painstaking work in noncultured primary tumors and in careful in vitro overexpression studies over the last 4 years demonstrated that the mechanism of PTEN inactivation can be varied and might be cell type dependent. Furthermore, apart from sporadic endometrial carcinoma, PTEN alteration in noncultured sporadic neoplasias likely occurs “late,” promoting progression and metastasis. The article by Davies et al. (Clin Cancer Res., 8: 1904–1914, 2002) sheds light on all of these issues when they report on data that derive from a “triple threat” strategy, i.e., in vitro, in vivo, and ex vivo, to demonstrate that adenoviral infection of PTEN into PTEN-null PC3 prostate cancer cell lines results in decreased metastatic potential without significantly altering tumor size via the predominant mechanism of G₁ cell cycle arrest but not apoptosis.

Introduction
In this issue of Clinical Cancer Research, Davies et al. (1) use an “in vitro-in vivo-ex vivo” system to demonstrate that adenoviral infection of the tumor suppressor gene PTEN into the PTEN-null PC3 prostate cancer line results in decreased metastatic potential without altering tumor size. A literature search using “PTEN” as a keyword reveals at least 721 publications, spanning such broad topics as normal development, glycemic control, cardiovascular disease, and carcinogenesis. Is PTEN a molecule for all seasons?

The important discovery of PTEN is intimately tied to the seemingly obscure story of the inherited hamartoma-tumor syndromes. The first putative locus for an inherited hamartoma syndrome, CS (3) (MIM 158350), characterized by multiple hamartomas and a risk of breast and thyroid cancers, was mapped to 10q22–q23 in 1996 (2). PTEN/MMAC1/TEP1 (MIM 601728) was isolated by three different groups (3–5). Using positional cloning strategies, two groups isolated PTEN/MMAC1 at 10q23.3 (3, 4). The third group isolated TEP1 when searching for molecules with homology to protein tyrosine phosphatases (5). By nucleotide and predicted protein sequence alone, PTEN was shown to have a large region of homology to chicken tensin and bovine auxilin and a protein tyrosine-phosphatase domain.

Protein PTEN: One Gene—Many Syndromes
Because the putative locus for CS was mapped previously to 10q22–q23, PTEN became an excellent candidate susceptibility gene. Germ-line mutations in PTEN have been identified in 80% of probands with CS (6, 7). Subsequently, germ-line PTEN mutations were found in 60% of patients with Bannayan-

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3 The abbreviations used are: CS, Cowden syndrome; PS, Proteus syndrome; MMAC, mutated in multiple advanced cancer; PTEN, phosphatase, tensin homologue, deleted on chromosome ten; TEP1, transforming growth factor-β-induced epithelial cell-derived protein tyrosine phosphatase; PI3K, phosphatidylinositol 3-kinase.
Role of PTEN in Neoplasia

Sporadic Carcinogenesis?

In the case of endometrial carcinomas, somatic mutations and allelic loss of PTEN are frequent, as further somatic genetics were performed, it became evident that somatic mutation and allelic loss of PTEN are seen in a subset of endometrial carcinomas and glioblastoma multiforme harbored frequently, perhaps even in normal-appearing glands (20). In contrast, somatic mutation and allelic loss of PTEN in brain tumors of the glioneural line occurs with any frequency only in glioblastoma multiforme, the highest grade among these tumors (19). Interestingly, in a proportion of solid tumors that have a low frequency (<10%) of somatic intragenic PTEN mutation, epigenetic (i.e., beyond genetic) silencing of PTEN can be a major mechanism of inactivation, e.g., melanomas (21), and in thyroid tumors and islet cell tumors, perhaps inappropriate subcellular compartmentalization (22–24). In other words, multiple mechanisms of somatic PTEN inactivation occur depending on the type of neoplasia involved.

PTEN in Prostate Carcinogenesis—Master Switch for Metastasis?

Apart from rare exceptions, i.e., endometrial carcinomas, it would appear that somatic PTEN mutations and deletions occur as a late event in the majority of noncultured solid tumors. The human in vivo data for sporadic adenocarcinomas of the prostate are no different. Overall, the intragenic mutation frequency averages 40% whether in cultured or noncultured prostate cancers. However, it would appear that loss of PTEN expression, believed to be secondary to promoter hypermethylation, tends to occur in advanced prostate cancers (28). Furthermore, the highest frequencies of 10q loss of heterozygosity and biallelic structural alterations occur in metastatic prostate cancer samples (25, 26). Indeed, complete loss of PTEN protein expression in noncultured primary prostate cancers was shown to be associated with a high Gleason score of 7 or higher and with advanced pathological stage (American Joint Committee on Cancer T3b and T4; Ref. 29). In other words, a nonworking PTEN is associated with poor outcome, and in prostate cancer, poor outcome is always tied with metastasis.

In this issue of Clinical Cancer Research, Davies et al. (1) report on data from experiments planned by leaping from the stage set by the genetic and molecular pathology data described above, and the historical observation that reintroduction of the human 10q23–q25 region into rat prostate cancer cells failed to alter tumorigenicity but significantly inhibited metastatic potential (30). The investigators use the PC3 prostate cancer model, which is known to be PTEN null. When they infected PC3 with an adenoviral construct harboring wild-type PTEN, phosphorylation of the proapoptotic factor Akt/PKB was inhibited, an observation similar to that seen after ectopic expression of PTEN in a variety of cell lines, whether PTEN wild-type or null [Refs. 31–35; reviewed by Waite and Eng (15)]. This downstream consequence is consistent with the known lipid 3-phosphatase activity of PTEN, which dephosphorylates its major substrates, phosphoinositide-3,4,5-triphosphate and phosphoinositol-4,5-diphosphate, thus acting in opposition to PI3K [Refs. 36, 37; reviewed by Waite and Eng (15)]. The Akt/PKB pathway lies downstream of the PI3K pathway. Therefore, when PTEN is wild type and functional, phosphorylation of Akt is inhibited. Depending on cell type, functioning PTEN induces cell cycle arrest at G1 and/or apoptosis, which are mediated by the D cyclins and p27 [reviewed by Waite and Eng (15)]. Davies et al. (1) demonstrate that the mechanism involved in their models is G1 arrest and not apoptosis.

Of significance, Davies et al. (1) have demonstrated in vitro, in vivo, and ex vivo that introduction of wild-type PTEN into established PC3 cells decreased metastatic potential but did

Somatic PTEN Alterations—Master Molecule for Sporadic Carcinogenesis?

Somatic PTEN mutations have been found, to a greater or lesser extent, in a wide variety of solid tumors and hematological malignancies, with the highest frequencies observed in cell lines. A review of the literature by Bonneau and Longy (16) found 332 somatic PTEN mutations in primary tumors and metastases. Initial work performed mainly on cell lines suggested a high frequency of intragenic somatic mutations, homozygous deletions, and biallelic loss of PTEN (3, 17). However, as further somatic genetics were performed, it became obvious that in noncultured primary solid tumors, only endometrial carcinomas and glioblastoma multiforme harbored frequent somatic mutations and biallelic structural alterations (18, 19). In the case of endometrial carcinomas, somatic PTEN mutation or epigenetic silencing occurs as one of the earliest events, perhaps even in normal-appearing glands (20). In contrast, somatic mutation and allelic loss of PTEN in brain tumors of the glioneural line occurs with any frequency only in glioblastoma multiforme, the highest grade among these tumors (19). Interestingly, in a proportion of solid tumors that have a low frequency (<10%) of somatic intragenic PTEN mutation, epigenetic (i.e., beyond genetic) silencing of PTEN can be a major mechanism of inactivation, e.g., melanomas (21), and in thyroid tumors and islet cell tumors, perhaps inappropriate subcellular compartmentalization (22–24). In other words, multiple mechanisms of somatic PTEN inactivation occur depending on the type of neoplasia involved.
PTEN-based Therapy for Prostate Cancer?

This study proposes an important therapeutic tool for the treatment of prostate cancer: gene therapy with exogenous wild-type PTEN. The authors also provide some evidence that combined therapy with wild-type PTEN and TP53 for prostate cancers, which are presumably PTEN and p53 deficient, might not have an increased incidence of prostate cancer (10).

References


4 C. Eng et al., unpublished observations.


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