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 germline or compound heterozygous genetic alterations from solid tumors or hematological malignancies, had a frequency of a variety of cancer cell lines, whether derived from solid tumors or hematological malignancies, had 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 Gi 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 syndrome. The first putative locus for an inherited hamartoma syndrome, CS (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 comparison, 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...

Protein PTEN: One Gene—Many Syndromes

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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.
Riley-Ruvalcaba syndrome (MIM 153480; Ref. 8) and in a proportion of individuals with PS (MIM176920) and Proteus-like syndromes (9). CS is an autosomal dominant inherited cancer syndrome characterized by multiple hamartomas and risks of breast, thyroid, and endometrial neoplasias (10). Bannayan-Riley-Ruvalcaba syndrome is characterized by macrocephaly, lipomatosi, hemangiomatosi, and speckled penis (11). PS is characterized by hamartomas, lipomas, and overgrowth with a mosaic distribution of affected tissues (12). Because it is of sporadic occurrence and mosaic distribution, many originally believed that either somatic mutation or germ-line mosaic mutation to be its origin, hence, the significance of finding germ-line PTEN mutations in a subset of PS (9). Remarkably, germ-line mutations in PTEN have been found in an individual with hydrocephaly with VATER (vertebral and anal malformations, tracheoesophageal atresia, and radial and renal malformations) association (13) and an individual with megalencephaly and autistic features (14). It has been suggested that syndromes that are characterized by the presence of germ-line PTEN mutations may be grouped by molecular definition and referred to as the PTEN hamartoma-tumor syndromes (8). Thus, PTEN hamartoma-tumor syndromes encompass PTEN mutation-positive cases regardless of the presenting clinical syndrome. This molecular-based diagnosis is important because it impacts clinical surveillance recommendations: presence of a germ-line PTEN mutation irregardless of syndrome name, even in syndromes that, in the past, were not known to be associated with cancer risk, should trigger the clinician to institute cancer surveillance similar to those recommended for CS (10). Similar to most tumor suppressor genes, the spectrum of mutations includes truncating and missense mutations scattered throughout the gene [reviewed by Waite and Eng (15)]. In at least one large series of CS probands, approximately two-thirds of the mutations were in exons 5, 7, and 8, with 40% within exon 5, although this exon only represented 20% of the coding sequence of the gene (7). Exon 5 encodes the phosphatase core motif, and the preponderance of mutations in that exon reflects the biology.

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 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 ranges from 0% to >60%, with those in the 40–65% range for prostate cancer cell lines (17, 25–27). Loss of heterozygosity 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 phosphoinositide-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
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 gene therapy with wild-type PTEN and TP53 for prostate cancers, which are presumably PTEN and p53 deficient, might provide an additive effect. Although gene therapy has captured the imagination of scientist, clinician, and lay public alike for several decades, there has yet to be a gene-based therapy that has been successful and used as clinical routine to treat cancer.

Thus, aside from choice of vectors, proposing PTEN as gene therapy requires budding gene therapists to consider the following. If wild-type PTEN is introduced into a tumor with a mutant PTEN, would the resultant dominant-negative effect (39) cause more harm? Furthermore, if the data in the Davies et al. (1) report is correct, then would the presence or the introduction of wild-type PTEN into prostate cancer metastases (which raises other issues as well) prevent more metastases because it presumably would not shrink existing metastases? Given the data presented in their report and the natural history of resected localized, early-stage prostate cancer, then it would also seem inappropriate to use PTEN gene therapy in early stages. So when would PTEN gene therapy be used for prostate cancer? Nonetheless, proposing an “upstream” (i.e., PTEN) replacement therapy may hold further promise than targeting downstream of a dysfunctional PTEN. Many have believed that PTEN-mediated growth suppression is only mediated by its lipid phosphatase activity and thus have proposed targeting downstream of the lipid phosphatase activity (40). However, because there is accumulating evidence that PTEN-mediated growth suppression is also dependent on its protein phosphatase activity and could be independent of PI3K/Akt [reviewed by Waite and Eng (15)], such downstream targeting either might not be 100% efficacious or might even cause harm.

References


in the PTEN tumour suppressor gene and a subset of Proteus syndromes.


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