TREK-1 is a two-pore domain (K_{2p}) potassium channel that carries a leak current that is time- and voltage-independent. Recently, potassium channels have been related to cell proliferation and some K_{2p} family channels, such as TASK-3, have been shown to be overexpressed in specific neoplasms. In this study, we addressed the expression of TREK-1 in prostatic tissues and cell lines, and we have found that this potassium channel is highly expressed in prostate cancer but is not expressed in normal prostate nor in benign prostatic hyperplasia. Furthermore, expression of TREK-1 correlates strongly with the grade and the stage of the disease, suggesting a causal link between channel expression and abnormal cell proliferation. In vitro studies showed that TREK-1 is highly expressed in PC3 and LNCaP prostate cancer cell lines but is not detectable in normal prostate epithelial cells (NPE). In this report, we show that overexpression of TREK-1 in NPE and Chinese hamster ovary (CHO) cells leads to a significant increase in proliferation. Moreover, the increased cell proliferation rate of PC3 cells and TREK-1 overexpressing CHO cells could be reduced when TREK-1 current was reduced by overexpression of a dominant-negative TREK-1 mutant or when cells were exposed to a TREK-1 inhibitor. Taken together, these data suggest that TREK-1 expression is associated with abnormal cell proliferation and may be a novel marker for and a molecular target in prostate cancer. [Cancer Res 2008;68(4):1197–203]

Introduction
Prostate cancer is the most commonly diagnosed cancer in the U.S. male population with >234,000 new cases anticipated in 2006 (1). In spite of advances in detection and treatment, prostate cancer is still expected to kill nearly 30,000 Americans this year. Thus, it is critical to develop new information about the cell biology of this cancer to permit the identification of novel molecular targets relevant to the disease. Over the last decade, research has shown that malignant prostatic epithelium undergoes a curious change in the expression of 15-lipoxygenase (15-LOX), an enzyme that metabolizes polyunsaturated fatty acids to hydroperoxy metabolites (2–5). Normal prostatic tissue expresses 15-LOX-2, which uses arachidonic acid as its preferred substrate and generates 15-hydroxyeleostearoic acid (HETE). However, malignant epithelium expresses 15-LOX-1, which uses linoleic acid as its preferred substrate and generates 13-hydroxyoctadecadienoic acid (HODE). This isomerase switch is highly correlated with Gleason score (6) and heterologous overexpression of 15-LOX-1 increases the tumorigenicity of cultured prostate cancer cells (7). The modification of the lipoxygenase "phenotype" suggested to us that it might be fruitful to investigate potential targets for the altered lipid metabolites that exist in prostate cancer cells.

One potential set of targets is the two-pore domain potassium (K_{2p}) channels. K_{2p} channels are a family of channels that carry background or "leak" currents (8, 9). Unlike other members of the potassium channel superfamily, each monomeric subunit of the K_{2p} channel carries two pore-forming loops, and thus, a complete channel is formed by dimerization. These channels are widely expressed and have been most intensely studied in neurons where they are thought to play an important role in regulating excitability by controlling the resting membrane potential. Recently, one member of the family, TASK-3, has been shown to be overexpressed in breast cancer (10), and heterologous expression of this potassium channel can confer an oncogenic potential to C8 mouse fibroblasts (11). In other studies, TASK-1 has been shown to play a role in neuronal apoptosis, (12) further suggesting that K_{2p} channels might have some role as modulators of cell proliferation. The mechanism by which potassium channels might alter the proliferative state of cells has been an open question for several years. Nevertheless, there is an accumulation of data that seems to link these channels with cancer (13–17).

In this study, we have focused on a lipid-sensitive member of the K_{2p} channel family, TREK-1. This channel, as most members of the K_{2p} family, is an open rectifier that is voltage- and time-independent. TREK-1 is regulated by phosphorylation (18) and activated by unsaturated fatty acids, such as arachidonic acid (19, 20). We found that TREK-1 is activated by the 15-LOX-2 metabolite, 15-HETE, and inhibited by the 15-LOX-1 metabolite 13-HODE. Thus, we thought that the differential regulation of TREK-1 by the different lipid metabolites in normal or malignant prostate epithelium might alter the function of this channel and result in changes in cell proliferation. To address the possible role of this channel in prostate cancer, we have investigated the expression of TREK-1 in human prostate tissues as well as in various cell lines including normal prostate epithelium (NPE) and PC3, a prostate cancer cell line. In addition, we have heterologously overexpressed TREK-1 and used a dominant-negative TREK-1 (dnTREK-1) to knock down its endogenous expression and evaluated the effect of these changes on proliferation in NPE and PC3 cell lines.
Materials and Methods

Cell culture. NPE cells were obtained from Cambrex and cultured in basal medium (Clonetech PrEGM; BulletKit), optimized by the provider. Human prostate cancer cell lines (PC3 and LNCaP) were obtained from American Type Culture Collection (ATCC) and were cultured in RPMI 1640 (Invitrogen), supplemented with 10% fetal bovine serum (FBS), and 4.5 g/L glucose. Chinese hamster ovary (CHO) cells were also obtained from ATCC and maintained in Ham’s F-12 supplemented with 10% FBS and 2 mmol/L l-glutamine.

Western blot analysis. TREK-1 protein was detected in the membrane fraction of the cells. For this purpose, cells were washed with PBS and then immediately transferred to ice-cold homogenization buffer [20 mmol/L HEPES (pH 7.6), 250 mmol/L sucrose, 2 mmol/L EDTA, 50 μg/mL aprotinin, 48 μg/mL leupeptin, 5 μmol/L pepstatin A, 1 μmol/L phenylmethylsulfonyl fluoride, 0.1 mmol/L sodium vanadate, and 50 mmol/L NaF]. Cells were lysed by sonication, and the membrane fraction was purified by centrifugation at 185,000 × g for 1 h at 4°C. Pellets were dissolved in homogenization buffer containing 1% Triton X-100, and proteins (20 μg) were separated by SDS-PAGE on an 8% gel. Samples were blotted onto nitrocellulose (Bio-Rad), and the membrane was blocked with 5% nonfat dry milk in TBS/0.1% Tween 20. TREK-1 was detected with a commercial monoclonal antibody (Vector Laboratories) at a 1:5,000 dilution. Staining and quantitation were done as above, except the slides were incubated with a biotinylated anti-mouse immunoglobulin at 1:25 dilution (Vector Laboratories) for 30 min. Diaminobenzidine was used as the chromogen and hematoxylin as a nuclear counterstain. The immunoreactivity for TREK-1 was scored, considering both the percentage of cells displaying a positive immunostaining profile [from undetectable (0%) to homogeneous expression (100%)] and the intensity of the staining (from 0, 1+, 2+, and 3+).

In addition, PC3 cells or PC3 cells expressing dnTREK-1 were screened for the proliferation marker Ki-67 using a mouse monoclonal antibody (Vector Laboratories) at a 1:5,000 dilution. Staining and quantitation were done as above, except the slides were incubated with a biotinylated anti-mouse immunoglobulin at 1:1,000.

Plasmid and adenviral constructs. The clone for human TREK-1 was originally a gift from Steven A.N. Goldstein (University of Chicago Comer Children’s Hospital, Chicago, IL; ref. 21) and has subsequently been subcloned into pDCS16 (hTREK-1) for mammalian expression. A dnTREK-1 mutant was created from the hTREK-1 plasmid by the introduction of two point mutations in the selectivity filter of the pore region (G161E and G268E). The mutations were introduced using the QuikChange kit (Stratagene). The primers designed to generate the mutation of G161 to E were 5'-CCATAGGATTTGAGAACATCTCACCACCGC-3' (forward) and 5'-GGGTGGTGAGATGTTCTCAAATCCTATGG-3' (reverse), and 5'-CTCTAACAATATTGAAATTGTTGGTACATGTTGC-3' (forward) and 5'-GCAACGCCAATTTCAATAGTTGGTACAG-3' (reverse) for G268E. This mutant channel expresses well but carries no current when expressed in CHO cells.

A human TREK-1 containing adenovirus (adTREK-1) was made using the AdMax kit (Microbiex Biosystems) according to the manufacturer's instructions. Briefly, the human TREK-1 coding sequence was subcloned into a shuttle vector, pDCS16 (hTREK-1) for mammalian expression. A successful recombination was achieved by transfecting the plasmid carrying pEHEK293s into a Shuttle vector, pDCS16. The resulting plasmid was cotransfected into E1-complementing HEK293 cells along with 35.5-kb E1-deleted Ad adenoviral genomic plasmid pBHGGtrDE1.3FLP. A successful recombination of adenoviral construct was amplified, harvested, and CsCl purified.

Cell transfection. Twenty-four hours before transfection, cells were seeded into six-well plates at 80% to 90% of confluence. Transient transfections were typically carried out with 1 μg of the plasmid carrying the channel cDNA and 12 μL GeneJammer (Stratagene) according to the manufacturer's instructions. Cells were cotransfected with pEGFP-C1 vector (Clontech) in a 1:1 ratio. After a 3-h incubation in Opti-MEM (Invitrogen), full-culture medium was applied. Forty-eight hours after the transfection, the cells were checked under the microscope for green fluorescence, and these were then used for patch-clamp experiments and cell proliferation assay (see below). NPE were infected with the adTREK-1 virus at a ratio of 1:25 dilution (Vector Laboratories) for 30 min. Diaminobenzidine was used as the chromogen and hematoxylin as a nuclear counterstain. The immunoreactivity for TREK-1 was scored, considering both the percentage of cells displaying a positive immunostaining profile [from undetectable (0%) to homogeneous expression (100%)] and the intensity of the staining (from 0, 1+, 2+, and 3+).
multiplicity of infection of 10. Cells were exposed to the virus for 4 h, after which they were placed into fresh growth medium. A green fluorescent protein–containing virus was used as a control for infection. Cells were tested 48 h after infection.

**Cell proliferation assay.** Cell proliferation was measured by a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (Roche) according to the manufacturer’s instructions. Cells were suspended in RPMI without phenol red and plated at \(1 \times 10^5\) cells per well in 96-well plates in growth medium and allowed to attach for 4 h for CHO and PC3, and 24 h for NPE cells. Cells were then grown for 18 h before the MTT reagent was added. In some cases, cells were treated with the TREK-1 blocker, sipatrigine (1–100 \(\mu\)mol/L; a gift of GlaxoSmithKline), during the 18th h. Sipatrigine was prepared as a stock solution (1,000 \(\mu\)mol/L) in DMSO and diluted in medium before application to the cells. The final concentration of DMSO never exceeded 0.1% and had no effect on either TREK-1 current or on the rate of cell proliferation. The MTT reagent was then applied for 4 h, and the resulting formazan crystals were dissolved overnight. The result was measured on an automated plate reader EL312e (Bio-Tech Instruments) set to record absorbance at 550 nm. All assays were done in triplicate. The results were confirmed in at least five independent experiments.

**Cell cycle analysis.** CHO cells were seeded into 10-cm diameter dishes (\(10^5\) cells per dish) in F12 medium and cultured for 24 h. The cells were transfected with TREK-1 as described above and, 48 h later, were stained with propidium iodide (Sigma) and then analyzed by flow cytometry using a FACScanBibur instrument (Becton Dickinson). Data were analyzed using the CELLQuest program (Becton Dickinson) to assess cell cycle distribution pattern (G0-G1, S, and G2-M phases).

**Electrophysiology: voltage clamp recordings and solutions.** Cultured cells (CHO, NPE, PC3, and LNCaP) were resuspended in an enzyme-free cell dissociation buffer (Life Technologies) and then plated on glass coverslips 1 to 2 h before starting the recordings. Coverslips were placed into a perfusion chamber mounted on the stage of an inverted microscope and superfused at room temperature with an external solution containing, for CHO cells (mmol/L): NaCl, 140; KCl, 5; CaCl\(_2\), 1; MgCl\(_2\), 1; HEPES, 5; and glucose, 10, adjusted to pH 7.4; for PC3, LNCaP, and NPE cells (mmol/L): NaCl, 140; KCl, 5; HEPES, 10; CaCl\(_2\), 2; MgCl\(_2\), 2; glucose, 5; Na\(_2\)HPO\(_4\), 0.3; KH\(_2\)PO\(_4\), 0.4; NaHCO\(_3\), 4; TEA-Cl, 10; CsCl, 5; methanandamide, 10 \(\mu\)mol/L; and nifedipine, 5 \(\mu\)mol/L adjusted to pH 7.2. Recordings were made using borosilicate glass pipettes with a tip resistance between 4 and 7 MΩ and filled with a solution containing, for CHO cells (mmol/L): aspartic acid, 130; KOH, 146; NaCl, 10; CaCl\(_2\), 2; EGTA, 5; HEPES, 10; and MgATP, 2 adjusted to pH 7.2; for PC3, LNCaP, and NPE cells (mmol/L): potassium glutamate, 140; Mg ATP, 0.1; EGTA, 8; HEPES, 5; CaCl\(_2\), 0.5; and MgCl\(_2\), 1 adjusted to pH 7.2. Two different voltage clamp protocols in whole cell configuration were used: for CHO cells, a ramp protocol from −130 to +40 mV; for PC3, LNCaP and NPE cells, a step (800 ms) protocol from −120 to +70 mV in 10-mV increments from a holding potential of −20 mV was applied. Recordings were started after the current reached a stable baseline (usually 3–4 min after initial cell rupture). The protocols were generated using Clampex 8.0 software applied by means of an Axopatch 200-B and a Digidata 1200 interface (Axon Instruments). The current signals were acquired at 5 kHz and filtered at 1 kHz.

**Electrophysiology: data analysis.** TREK-1 current in PC3 and CHO cells was identified as the sipatrigine-sensitive current (22). The subtraction of the current measured in the presence of sipatrigine (50 \(\mu\)mol/L) from the current measured in control conditions results in an outward rectifying current. For all PIN and invasive prostatic

**Results**

**TREK-1 is overexpressed in human prostate cancer.** Immunohistochemical studies performed on a control CHO cell line overexpressing TREK-1 revealed an intense and homogeneous nuclear staining for the channel (data not shown). Analyses of normal prostate and BPH samples (\(n = 23\)) revealed that TREK-1 expression was undetectable in luminal epithelial cells and stromal elements (Fig. 1A). We observed that 78% of nontumor tissue samples displayed a weak (+) and heterogenous TREK-1 expression in basal cells. However, all PIN and invasive prostatic
carcinomas were found to express the channel in a high proportion of tumor cells. More specifically, we found that low-grade PIN lesions had a heterogeneous expression pattern of TREK-1, displaying between 20% and 40% positive tumor cells with mild-to-moderate (1+ to 2+) nuclear immunoreactivity (Fig. 1B). In contrast, high-grade PIN lesions were found to express TREK-1 in 60% to 100% of the tumor cells, with high (3+) immunostaining intensity. All invasive prostatic carcinomas studied (n = 33) were found to display a TREK-1–positive phenotype (Fig. 1C–D). Well-differentiated, low Gleason score cases (Gleason score < 7) tended to be more heterogeneous and weak in the intensity of the immunostaining [30–60% of cells overexpressed the channel with a moderate (2+) intensity], whereas the remaining cases displayed a more homogenous and intense TREK-1 expression pattern [60–100% positive tumor cells with a moderate (2+) to high (3+) immunostaining]. To evaluate whether the overexpression of TREK-1 might be a characteristic of prostate cancer and could play a role in control of cell proliferation, we first studied the expression of TREK-1 in cultured NPE and in two well-established prostate cancer cell lines, PC3 and LNCaP. Western blot analysis showed a striking difference between NPE, which did not express detectable levels of TREK-1 protein, and the two cancer cell lines that expressed high levels of the protein (Fig. 2A).

**Endogenous TREK-1 expression contributes to cell proliferation in PC3 cells.** To determine if endogenous TREK-1 expressed in PC3 cells was functional, patch-clamp experiments were undertaken. PC3 cells had a robust basal TREK-1 current, which averaged 3.3 ± 1.0 pA/pF at +70 mV (Fig. 2B and D). Furthermore, this basal current could be activated by the application of arachidonic acid, which is typical for TREK-1 (23). Thus, the maximal current at +70 mV under these conditions was ~5 pA/pF (data not shown). This current was also detectable in LNCaP cells (data not shown).

In separate experiments, we created a dnTREK-1 mutant, which was generated by a double mutation in the ion selectivity filters of the pore region of the channel (11). When expressed in CHO cells, dnTREK-1 carried no current, and when it was coexpressed with wild-type TREK-1, dnTREK-1 completely blocked the expression of this current. Similarly, in PC3 cells, expression of dnTREK-1 completely ablated the endogenous current that was previously detected in these cells (Fig. 2C and D). We obtained similar results with LNCaP cells, although we did not investigate the properties of those cells in as much detail as the PC3 cells (data not shown).

Proliferation of PC3 cells was measured by an MTT proliferation assay and confirmed by Ki-67 immunohistochemistry. The effect of TREK-1 expression on proliferation was determined by comparing PC3 cells to cells that were transfected with dnTREK-1. Transfection with an enhanced green fluorescent protein (EGFP)-bearing plasmid was included as a control and had no effect on proliferation. In this experiment, the expression of dnTREK-1 caused a significant reduction (P < 0.05; repeated measures ANOVA) in proliferation rate (Fig. 3). Ki-67 immunohistochemistry corroborated the MTT assay of proliferation rate (data not shown). As expected, PC3 cells transfected with dnTREK-1 had significantly
fewer cells stained positive for Ki-67 (17%; $n = 149$) than control PC3 cells (53%; $n = 159$; $P < 0.0001$; Fisher’s exact test). These results suggested that expression of the TREK-1 current may play a regulatory role in cell proliferation.

**TREK-1 overexpression increases cell proliferation.** The proliferation rate of NPE cells is considerably slower than that of prostate cancer cell lines. In part, this may be due to the fact that the NPE cells express no measurable TREK-1 current (Fig. 4A and C). NPE can be induced to overexpress the channel by infecting them with an adTREK-1. adTREK-1 NPE cells express a substantial TREK-1 current (Fig. 4B and C) and display a significant increase in their cell proliferation rate as measured by the MTT assay (Fig. 5A). We found that sipatrigine, a TREK-1 inhibitor (22), significantly reduced the proliferation of adTREK-1 NPE cells (Fig. 5), thus confirming the importance of the current in the regulation of cell proliferation.

This finding was not unique to NPE cells as we could recapitulate these results in CHO cells. Overexpression of TREK-1 in CHO cells led to a significant increase in proliferation that was blocked by the TREK-1 inhibitor, sipatrigine, in a dose-dependent manner (data not shown). In fact, there is a strong positive correlation between sipatrigine-dependent inhibition of TREK-1 current and inhibition of cell proliferation (Fig. 5B; $P < 0.0001$). Although the effect on proliferation was not cell type dependent, it did depend upon the type of potassium channel expressed. For example, we also overexpressed Kir2.1 and TASK-1 in CHO cells and did not observe a significant increase in cell proliferation (data not shown). Consistent with the MTT results, we confirmed the effect of TREK-1 overexpression on proliferation by cell cycle analysis. CHO cells that overexpress TREK-1 showed a significant reduction in the number of cells in $G_0$ with a corresponding increase in cells in $S$ phase (Fig. 6).

![Figure 5](image1.png)

**Figure 5.** TREK-1 overexpression significantly increases and is correlated with the proliferation rate of NPE and CHO cells. A, NPE were infected with adTREK-1 or a control virus and, 24 h later, plated at equal densities ($1 \times 10^5$ cells per well). After 48 h, some of the cells (as noted) were treated with sipatrigine (5 $\mu$mol/L) for an additional 24 h before their cell proliferation was measured by an MTT assay. Results were normalized to the proliferation rate of NPE and expressed as the mean (n = 5) percent of control + SE. The means were compared by a repeated measures ANOVA. * $P < 0.001$ versus NPE and NPE/sipatrigine; ** $P < 0.001$ versus NPE/TREK-1. B, CHO cells were transfected with TREK-1 and then exposed to varying amounts of the TREK-1 blocker, sipatrigine. The level of inhibition of the current by sipatrigine was then plotted against the inhibition in the cell proliferation rate to generate the depicted regression analysis ($r = 0.8; P < 0.0001$).

![Figure 6](image2.png)

**Figure 6.** Effect of TREK-1 overexpression on the cell cycle. A, cell cycle analysis of the control CHO by fluorescence-activated cell sorting. Columns, mean number of cells in the different phases of the cell cycle, determined with Cell Quest program; bars, SD. These results are typical for three independent experiments. G0-G1, **$P < 0.001$**. B, cell cycle analysis 48 h after transient transfection of CHO with TREK-1 shows a significant decrease in the number of cells in G0-G1 phase (*** $P < 0.001$) and a corresponding increase in the number of cells in S phase (* $P < 0.01$). These results are typical for three independent experiments. A typical run is depicted in each inset.
Discussion

Numerous ion channels have been linked to the regulation of cell proliferation, and a growing list of these channels are now recognized to play a role in the development of cancer in various tissues. Interestingly, of the vast potassium channel family, only a few have been identified that alter cell proliferation (24–26). These include Kv1.3 and K<sub>2p</sub>3.1, which are particularly important for the regulation of proliferation in lymphocytes, along with Kv11.1 (HERG), Kv10.1 (Eag1), and K<sub>2p</sub>9.1 (TASK-3). Some of these channels are overexpressed in human cancers including melanoma, small cell lung cancer, breast cancer, colon cancer, neuroblastoma, and prostate cancer (27–33) and have been proposed to be oncogenes. Data presented in this study supports the addition of TREK-1 (K<sub>2p</sub>2.1) to this growing list of potassium channels whose abnormal expression is linked to cancer, in this case, prostate cancer. Thus, we have found that TREK-1 is expressed in human prostate cancers but not in normal prostate tissue, and that increased proliferation is induced by overexpression of this channel in normal cells. Conversely, inhibition of TREK-1 activity in cultured cancer cells whether by a nonspecific pharmacologic blocker or by a dominant-negative mutant of the channel reduces proliferation to a near normal level.

Although the activation of K<sup>+</sup> channels is required for progression of cells into G<sub>1</sub> phase of the cell cycle (12, 24, 34–38), the mechanism by which these channels regulate proliferation is not known. It has been proposed that it could be related to changes in the resting membrane potential or in cell volume (24), but changes in these variables would be an effect common to many types of potassium channels and not restricted to a small subset of this large family of proteins. An unexpected observation in our studies that may direct future mechanistic investigations has to do with the localization of the overexpressed TREK-1 protein. Although it is certain that a functional channel is present in the plasma membranes of our cells that overexpress TREK-1 because we could measure these channels by patch-clamp recording (Figs. 4 and 5), immunostaining showed a substantial expression of the TREK-1 protein in the nucleus, where it would not be expected to contribute to the regulation of either plasma membrane potential or cell volume. Therefore, further studies are required to determine the significance of TREK-1 expression in the nucleus.

An antiapoptotic role for TREK-1 has been suggested by Lang-Lazdunski et al. (39) who showed that activation of TREK-1 with rituxazole, a nonspecific channel activator, can prevent ischemic spinal cord injury, preventing cell death. The function of other two-pore domain channels has been linked to cell proliferation and death. Thus, Lauritzen et al. (40) reported a correlation between TASK-1 and TASK-3 activities in cultured neurons and neuronal apoptosis. Yet, other studies have suggested that overexpression of TASK-3 underlies malignant transformation in breast, lung, and colon cancers. TASK-3 has been found to be overexpressed in 44% of breast cancers and in 35% of lung cancers, and furthermore, 10% of breast cancers showed TASK-3 gene amplification (10). As in the case of TREK-1, the oncogenic ability of TASK-3 depends on the activity of the channel to carry a potassium current. Nonfunctional channels not only lose their tumorigenic capability but they can act as dominant negatives blocking the endogenous channel function and preventing the formation or tumors in nude mice (11).

In the present study, we found overexpression of TREK-1 protein in a high proportion of tumor cells in all PIN and invasive prostatic carcinomas and in both PC3 and LNCaP cell lines. These findings suggest that increased TREK-1 expression can occur at early stages in the development of prostate cancer. The high frequency of TREK-1 overexpression in prostate cancer along with its correlation with grade and stage of the disease suggests that this channel might be both a prostate tumor marker and a novel therapeutic target. Moreover, our results in prostate cancer make it of great interest to investigate the expression of TREK-1 in other types of cancer.

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TREK-1 Is a Novel Molecular Target in Prostate Cancer

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