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Advances in Brief

The t(6;16)(p21;q22) Chromosome Translocation in the LNCaP Prostate Carcinoma Cell Line Results in a *tpc/hpr* Fusion Gene[1]

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Abstract

Very little is known about the molecular and genetic mechanisms involved in prostate cancer. Previous studies have shown frequent loss of heterozygosity (40%) at chromosomal regions 8p, 10q, and 16q, suggesting the presence of tumor suppressor genes in these regions. The LNCaP cell line, established from a metastatic lesion of human prostatic adenocarcinoma, carries a t(6;16)(p21;q22) translocation. To determine whether this translocation involved genes important in the process of malignant transformation, we cloned and sequenced the t(6;16) breakpoint of this cell line. Sequence analysis showed that the breakpoint is within the haptoglobin gene cluster on chromosome 16, and that, on chromosome 6, the break occurs within a novel gene, *tpc*, similar to the prokaryotic S10 ribosomal protein gene. The translocation results in the production of a fusion transcript, *tpc/hpr*.

Introduction

Carcinoma of the prostate is the most frequent cancer in American males, and its incidence is increasing (1). Although very little is known regarding the molecular mechanisms involved in prostate tumorigenesis, a multistep process involving multiple genetic changes seems likely. Alterations of p53 (2), loss of DCC expression, and LOH[3] at the *DCC* locus (3) have been reported in prostate cancer, suggesting a possible role for these genes in the development and/or progression of this disease. Other, as yet, unidentified genes, possibly located at sites of observed chromosomal abnormalities, such as 2p, 7q, and 10q (4) may play a critical role in prostate cancer. In addition, LOH studies have suggested that putative tumor suppressor genes located at 8p22 (5, 6), 10q22-qter (7), and 16q22 may be involved in up to 65% of prostate cancers (5, 7, 8). Indeed, between 40 and 65% LOH has been detected at these chromosomal regions.

Loss of genetic material in tumor cells has been shown to be associated with the loss of tumor suppressor gene function. This region of chromosome 16, exhibiting allelic loss in prostate cancer, overlaps with regions of LOH described in breast cancer (9, 10), hepatocarcinoma (11), and Wilm's tumor (12), suggesting that the same tumor suppressor gene(s) may be involved in all of these tumors. A t(6;16)(p21;q22) translocation has been described in the LNCaP cell line (13), and similar translocations involving 16q22 have been described in fresh prostate tumor samples (14). To determine whether the translocation results in disruption of the putative tumor suppressor gene at 16q22, we decided to analyze the breakpoint at the molecular level. We have found that the translocation results in fusion of the *hpr* gene on chromosome 16 to the *tpc* gene, a novel gene coding for a protein similar to ribosomal protein S10.

Materials and Methods

Rodent-Human Hybrids. The hybrids series A9LN were obtained from the fusion of the human prostate carcinoma cell line LNCaP and the mouse A9 cell line as previously described (15). PCR analysis with primers from both the short and long arms of chromosome 16 was carried out in 1 × PCR buffer with $MgCl_2$ (Boehringer Mannheim) with 100 ng template DNA, 100 ng each of forward and reverse primer, 250 μM deoxynucleotide triphosphates (Perkin Elmer/Cetus), and 0.5 units of Taq DNA polymerase (Boehringer Mannheim) in a total volume of 50 μl. Thirty cycles of amplification were carried out at 55–60°C annealing temperature as appropriate for each primer. Human placental DNA (Oncor) and mouse DNA were used as controls. Primers 16AC1.1F/R at 16p11.2-q11.2, SM5BA/B at 16p13.3, 16AC6.21F/R at 16p12.2-q13, LCAT.PCR1.1/2 at 16q22.1, CALB2.PCR.1/2 at 16q22.1, 16AC7.46F/R at 16q22.2-q23.1, HP.PCR1.1/2 at 16q22.1, HPR1/2 at 16q22.1, HP.PCR2.1/2 at 16q22.1, and APRT.PCR1.1/2 at 16q24.2-qter were used to characterize the hybrids. The sequence of all oligonucleotide primers used for hybrid screening are available through the Genome Data Base.

Rodent-human hybrids containing chromosomes 16, 14, 8, 7, or 6 as the only human material were obtained from the National Institute of General Medical Science Human Genetic Mutant Cell Repository (Coriell Institute, Camden, NJ).

Cell Lines. Cell lines used in this study: LNCaP, DU145, and PC3 (prostatic carcinoma), SW48 (colon cancer), MCF7 (breast cancer), and W138 (fibroblastic) were obtained from American Type Culture Collection. Other cell lines [DEL (16), SU-DHL-1 (17), Karpas 299 (anaplastic large cell lymphoma; Ref. 18), and K9827F (lymphoblastoid; Ref. 19] were also used.

DNA Probes. Probes HPR, HP.PCR1, LNH, B4, and CL7G4 used in this study were obtained by PCR amplification of normal human DNA with primer sets HPRF/R, HP.PCR1.1/2, LNH.1/2, B4A2/3, and CL7G4/7, respectively. The sequence of the primers that were not obtained from Genome Data Base are listed in Table 1. The hp2α probe was obtained from American Type Culture Collection.

Southern and Northern Blot Analysis. DNA from cell lines and hybrids was digested with restriction enzymes (Boehringer Mannheim), electrophoresed, blotted on nylon membranes (Stratagene), and hybridized according to standard procedures (20).

Total RNA from cell lines and patient samples was extracted using the guanidinium thiocyanate method (21). Poly(A) RNA was purified with the PolyA Tract mRNA isolation system IV (Promega). Northern blot analysis was carried out with 1 μg Poly(A) RNA or 20 μg total cellular RNA. A Northern blot containing about 4 μg Poly(A) RNA from several normal tissues, including testis, colon, and spleen (Clontech), was also used.

Genomic Libraries. A size-selected genomic library was constructed by *Eco*RI digestion of LNCaP DNA. Digested DNA was electrophoresed through a 0.8% low-melting agarose gel. A band of the same size as the rearranged fragment detected by Southern blot analysis of LNCaP DNA with the HPR probe was cut from the gel. The DNA was eluted by agarase treatment (Boehringer Mannheim) and packaged in λ phage DASH II (Stratagene). The library was screened by standard plaque lifts with the HPR probe.

A phage library was constructed in EMBL3 (Stratagene) by partial Sau3AI digestion of DNA from a chronic lymphocytic leukemia sample which did not

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[3] The abbreviations used are: LOH, loss of heterozygosity; ORF, open reading frame; HP, haptoglobin; *hpr*, haptoglobin related; tpc, translocated in prostate cancer.

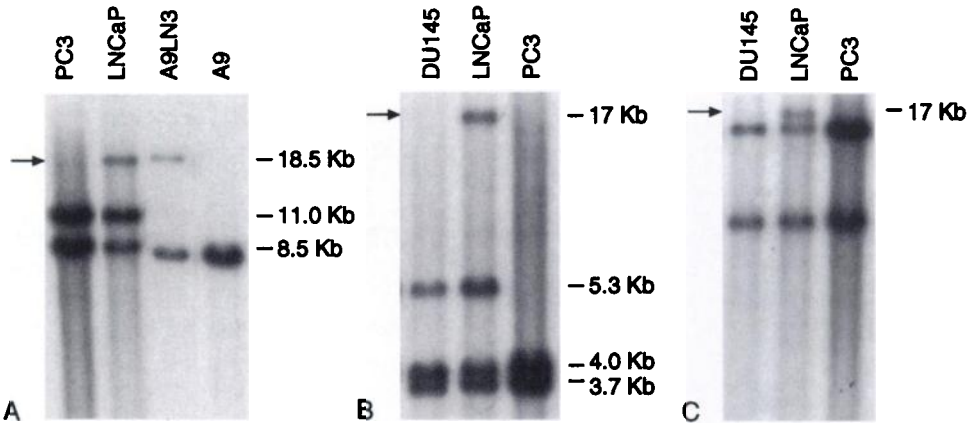

Fig. 1. Southern blotting analysis with chromosome 6 (B4) and chromosome 16 (HPR) probes detecting the rearrangement in the LNCaP cell lines. *A*, *Eco*RI digest probed with HPR; *B*, *Hin*dIII digest probed with HPR; *C*, same blot as in *B*, probed with B4. *Arrows*, rearranged restriction fragments present in the LNCaP cell line and in the A9LN3 hybrid. Previously described HP polymorphisms detected with *Eco*RI (11-kb restriction fragment, *A*) and *Hin*dIII (4 and 5.3 kb, *B*) are clearly apparent in cell line DNAs.

show any evidence of rearrangement with the B4 probe. The library was screened with the B4 probe to obtain germline genomic clones from *tpc*.

cDNA Libraries. A normal human liver cDNA library (Clontech) was screened using standard plaque lifts with the B4 probe (Table 1). One of two positive phage clones was subcloned into pBluescript KS(+) and sequenced as described below.

A cDNA library of LNCaP mRNA was constructed in the λ ZAP Express vector (Stratagene) and screened using standard plaque lifts with the B4 probe. Eight clones were isolated from the library and sequenced.

Sequencing and Sequence Analysis. DNA fragments were sequenced by the dideoxynucleotide termination reaction chemistry for sequence analysis on the Applied Biosystems Models 373A and 377 DNA sequencing systems.

Reverse Transcription PCR. One μg of total cellular RNA, 100 ng oligo(dT) primers, and 100 ng random hexamers primers (BRL) were first denatured for 10 min at 70°C, chilled on ice, and then incubated for 1 h at 37°C in 20 μl of a reaction mixture containing 1× first-strand buffer, 250 μM deoxynucleotide triphosphates (Boehringer Mannheim), 10 mM DTT, and 200 units Superscript II reverse transcriptase (BRL). One tenth of the reaction was used for PCR amplification with S11 and HPT3 primers (Table 1).

PCR products were separated in an agarose gel and purified by ion exchange columns (Qiagen) according to the manufacturer's instructions.

Results

Mapping of the Chromosome 16 Breakpoint in the t(6;16) Translocation. Karyotype analysis of the human prostatic cancer cell line LNCaP showed a t(6;16)(p21;q22) reciprocal translocation as well as other abnormalities involving chromosomes 2, 10, and 13 (13). To isolate the der(6) chromosome involved in the translocation, the LNCaP cell line was fused with the mouse A9 cell line deficient in *APRT*, a gene located at human chromosome 16. Resulting rodent-human hybrids were grown in selective medium (15) and analyzed cytogenetically and by PCR for the presence of the der(6) or der(16) chromosomes resulting from the translocation. Two of the hybrids, A9LN3 and A9LN5, contained the der(6) chromosome, but not the normal 16 or the der(16). Primers from the short arm and from the proximal long arm of chromosome 16, including HP.PCR1.1/2, did not amplify A9LN3 or A9LN5 DNA, suggesting these loci are centromeric to the chromosome 16 breakpoint. Primers from the distal long arm of chromosome 16, including HP.PCR2.1/2 and HPR.1/2, were present in the hybrids, suggesting that these loci are telomeric to the chromosome 16 breakpoint. Primers HP.PCR2.1/2 and HPR.1/2, are located in the telomeric end of the Hp complex. Primers HP-.PCR1.1/2, on the other hand, are located on the centromeric end of the *Hp* gene cluster. These results suggested that the breakpoint on chromosome 16 lies within the *Hp* gene cluster.

Cloning of the Rearranged Fragment Derived from the der(6) Chromosome. To confirm our finding, telomeric (HPR) and centromeric (HP.PCR1) DNA fragments derived from the normal *Hp* gene cluster were used as probes on Southern blots of LNCaP DNA. The HPR probe detected a rearranged *Eco*RI and a rearranged *Hin*dIII restriction fragment in the LNCaP cell line and in the A9LN3 and A9LN5 hybrids (Fig. 1). The HP.PCR1 probe, on the other hand, detected a rearranged *Eco*RI restriction fragment in the LNCaP DNA only. These results confirmed our previous finding and indicated the presence of two derivative chromosomes in the LNCaP cell line, one detected by the HPR probe and the other by the HP.PCR1 probe.

To clone the rearrangement and to identify the genes involved, we constructed a size-selected *Eco*RI genomic library from the LNCaP cell line and screened it with the HPR probe. A clone, E1, was selected for further studies. Restriction mapping analysis indicated that the breakpoint was contained within a 2.0-kb *Bam*HI fragment in clone E1. This fragment was subcloned into the plasmid vector pBluescript KS(−) and sequenced. Comparison between published *hpr* sequences and the sequence obtained from our fragment revealed that one end of this subclone contained 1.103 bp derived from *hpr* (Fig. 2). Identity with the *hpr* gene started at nucleotide 21,827 of germline *hpr* and continued downstream to the *Bam*HI site present in our subclone (nucleotide 22,820 of germline *hpr*). Upon close inspection of this stretch of homology, a deletion of 35 nucleotides (from 22,115 to 22,150 of germline *hpr*) was found in the LNCaP-derived clone (Fig. 2). In addition, within the LNCaP-derived clone, and immediately 5′ of the region of *hpr* identity described above, we found an insertion, with inversion, of 145 nucleotides derived from *hpr* sequences surrounding the 35 nucleotides that were deleted in our clone (Fig. 2). Sequence homology search through the GenBank data base, with the remaining 782 nucleotides of our subclone, revealed identity in 169-bp overlap to the human EST01826 (GenBank no. M78229) similar to ribosomal protein S10. The locus was named *tpc*.

To confirm the chromosomal origin of these sequences, PCR primers (B4A2/3, Table 1) were designed 5′ of the fusion point and used to screen a panel of somatic cell hybrids. A band of the expected size was detected only in the NA10629 hybrid containing chromosome 6 as its only human DNA content. In addition, primers (B8A and B13B, Table 1) were derived from either side of the fusion point and tested on LNCaP and normal human DNA. A PCR product of the expected size was detected only in the LNCaP cell line, confirming the authenticity of the cloned rearrangement. Probe B4 (Fig. 2) was obtained by amplification of chromosome 6-derived sequences present in the *Bam*HI subclone. B4 was hybridized to the same Southern blots previously used to detect the LNCaP rearrangement with the HPR probe. The B4 probe detected the same rearranged restriction fragments as the HPR probe (Fig. 1*C*).

Cloning of the Normal tpc Locus. Two germline *tpc* clones isolated from the CLL EMBL3 library were selected for further study.

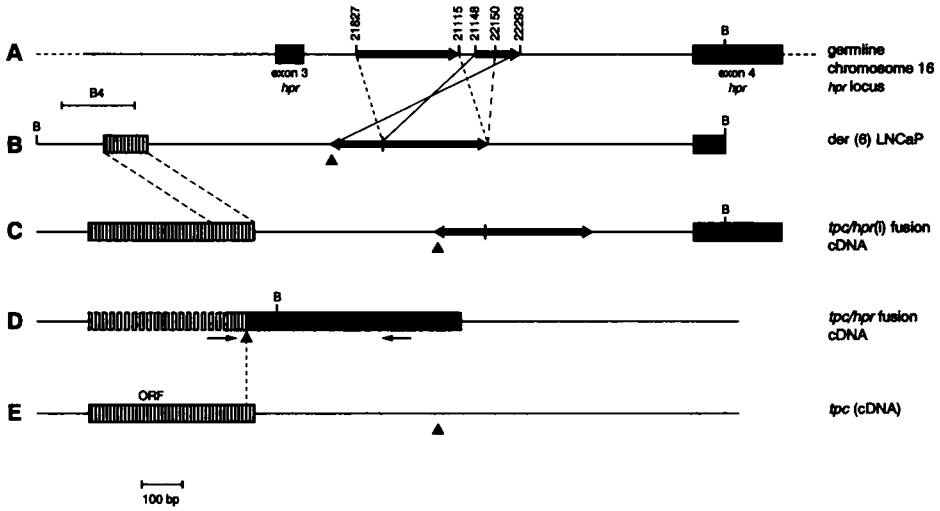

Fig. 2. Schematic representation of cDNA and genomic breakpoint regions. *A*, germline *hpr* locus. *B*, derivative (6) chromosome containing the translocation breakpoint from the LNCaP cell line. C, *tpc/hpr*(i) fusion cDNA containing intronic sequences. *D*, *tpc/hpr* fusion cDNA. *E*, normal *tpc* transcript. Coding sequences are represented as *striped boxes* (*tpc*) and *solid black boxes* (*hpr*). ▲, positions of cDNA and genomic breakpoints. *Numbers above A*, germline positions of nucleotides involved in the rearrangement of intronic *hpr* sequences which is depicted in *B* and *C*. *Thick arrows* in *A–C*, germline and rearranged orientation of intronic *hpr* sequences. *Thin arrows* in *D*, orientation and approximate position of oligonucleotide primers used for cloning of the *tpc/hpr* cDNA. The *letter B* in *A–D*, position of *Bam*HI sites.

Table 1 *Sequence of oligonucleotide primers used for the isolation of DNA probes and for the amplification of mRNA and genomic junction regions*

Primer name	Sequence	PCR product
B4A2	CTA TAG AAA GAC TAG GGG GA	B4 probe (ch[a]6)
B4A3	CTG AGG CTT TAT GAC TTG	
LNH1	CCA AGA ATC CGC CAA ACC CA	LNH probe (ch16)
LNH2	TGT GCT GCC TTC ATA ATG CG	
CL7G7	CCC TTA AAC TGC ATT GCC TA	CL7G4 probe (ch6)
CL7G4	AAA TTG CTG CTT TGC TGC AC	
S11	CCA ATC TGG GAA ACA CTA TC	*tpc/hpr* cDNA
HPT3	TAG ACA TGC CGA CAC AGA AG	
B8A	CAG GCT GGC ATA TGC TAA	Genomic fusion
B13B	CCT AAT AAC GAG AAG CAG	

[a] ch, chromosome.

Restriction mapping and sequence analysis indicated that the two clones combined contained the entire *tpc* ORF. Intron/exon boundaries in the region surrounding the fusion point in the cDNA were determined by sequencing of the genomic clones. Results indicate the presence of an exon beginning approximately 70-bp 5′ of the *tpc/hpr* cDNA fusion point and continuing into the 3′ untranslated region of *tpc*.

cDNA Cloning. Northern blot analysis of LNCaP RNA with the B4 probe indicated the presence of two abnormal transcripts (2.0 and 3.5 kb) in this cell line (Fig. 3). Three normal transcripts (2.2, 1.7, and 1.4 kb), detected by the B4 probe, which were present in all other cell lines and tissues tested, including testis, colon, and spleen, were also present in the LNCaP cell line.

To clone the normal *tpc* transcripts, a normal human liver cDNA library was screened with the B4 probe. Three clones of 2.2 kb were obtained, and one of these was sequenced. Sequence analysis showed the presence of an ORF of 477 nucleotides, encoding a protein of 159 amino acids. Comparison of our cDNA clone with EST01826 sequences revealed 98.7% identity in a 392 nucleotide overlap beginning 137 nucleotides downstream from the first ATG present in the *tpc* cDNA. Chromosome 6 and chromosome 16 (S11 and HPT3, Table 1) primers located on either side of the cDNA fusion point, as predicted based on known genomic structure, were used to amplify the fusion cDNA from the LNCaP cell line. An amplification product of 692 bp was obtained which was only present in the LNCaP cell line, indicating that the observed product derived from the t(6;16) translocation (Fig. 4*A*). The amplified cDNA was gel purified, sequenced, and shown to contain the mRNA breakpoint within frame fusion of *tpc* and *hpr* (Fig. 4*B*). A probe (LNH) derived from chromosome 16 sequences immediately 3′ of the mRNA fusion point detected transcripts in the LNCaP cell line only. Furthermore, the transcripts detected by LNH were of the same size (2.0 and 3.5 kb) as the LNCaP-specific transcripts previously detected with the B4 probe.

Both the 2.0- and 3.5-kb transcripts are therefore derived from the same chromosome (der6). No normal *hpr* or der16-derived transcripts were detected with probes specifically designed for this purpose (hp2α and CL7G4; Table 1), indicating that *hpr* is not normally expressed in any of the tissues or cell lines tested. In addition, the presence of a derivative 16 chromosome in the LNCaP cell line does not result in production of an *hpr/tcp* fusion mRNA.

To determine whether the two mRNAs observed using Northern blotting with the B4 probe result in the production of two different fusion cDNAs, we constructed a cDNA library from the LNCaP cell line and screened it with the B4 probe. Eight cDNA clones were isolated from the library, one of which, named *tpc/hpr*(i), contained

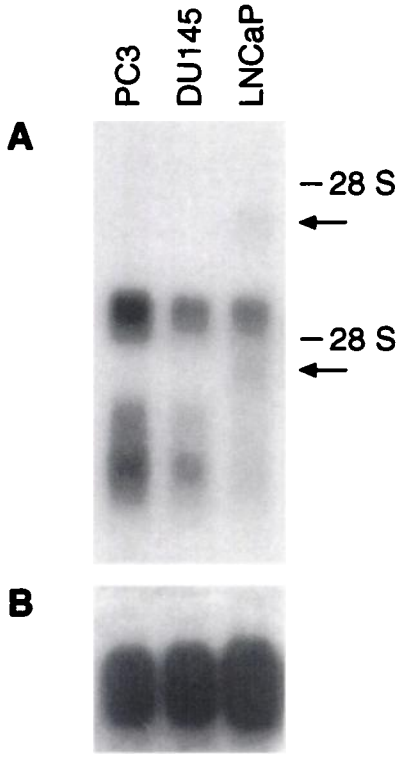

Fig. 3. Northern blot of poly(A) RNA from DU145, PC3, and LNCaP cell lines probed with B4 (*A*). *Arrows*, abnormal transcripts detected in LNCaP. The same blot probed with an actin cDNA (*B*).

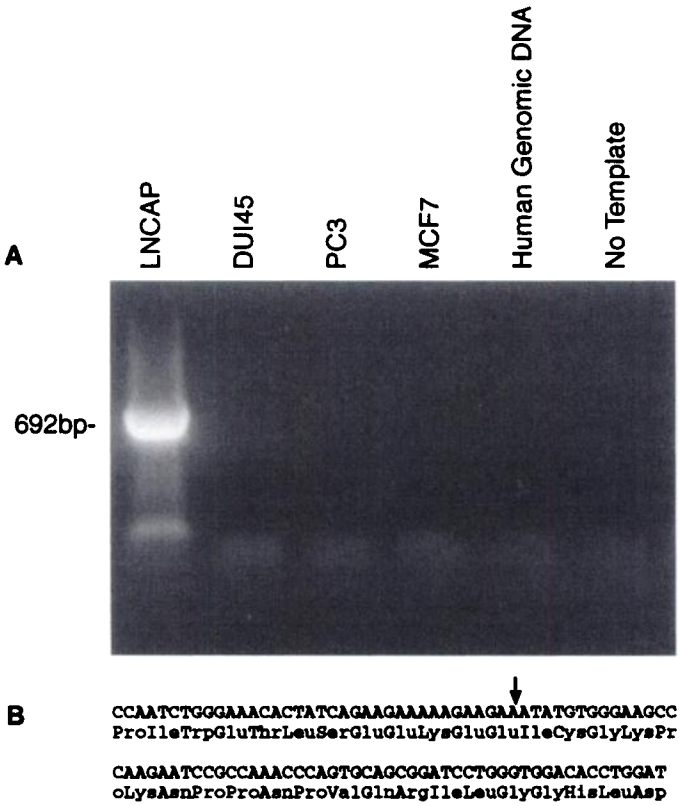

Fig. 4. PCR amplification of the *tpc/hpr* fusion cDNA (*A*). Sequence of the fusion transcript surrounding the breakpoint and predicted protein product (*B*). *Arrow*, cDNA fusion point.

hpr-derived sequences at one end and chromosome 6-derived sequences at the other.

Sequence analysis of *tpc/hpr*(i) indicated that the clone derived from a fusion mRNA that contains intronic sequences identical to those present in the der(6) chromosome (Figs. 2 and 5). The presence of Alu repeats within the intronic region retained in *tpc/hpr*(i) preclude the use of this fragment as a probe on Northern blots. However, size comparison of the two abnormal transcripts present in the LNCaP cell line suggests that *tpc/hpr*(i) cDNA corresponds to the larger transcript and that the in-frame *tpc/hpr* fusion cDNA cloned by PCR corresponds to the smaller transcript.

Discussion

Recurrent chromosomal translocations have been shown to play a role in the etiology of most hematopoietic tumors and a few solid malignancies. It is thought that these rearrangements result in the activation of cellular oncogenes and, infrequently, in loss of function of tumor suppressor genes. In leukemias and lymphomas, several proto-oncogenes are activated by translocation which result in either their deregulation or in the formation of oncogenic chimeric proteins (22–24).

Chromosome 16 at band q22 has been shown to be involved by rearrangements in several different neoplasias. The inversion (inv)(16)(p13;q22) and related t(16;16)(p13;q22) translocation, originally described in a subtype of acute myelomonocytic leukemia, have been shown to result in the fusion of the *CBFβ* gene, a transcription factor, with the myosin heavy chain gene (*MYHII*), and in production of a *CBFβ/MYHII* chimeric transcript (25). Cytogenetic studies of breast tumors indicate the involvement of chromosome 16 at bands q22–q24 as an early event in breast carcinogenesis (26). LOH at 16q22 has been correlated with distant metastasis (27), and at least two distinct regions are likely sites of tumor suppressor genes (9). The same chromosomal region, 16q22, is also lost in Wilm's tumor (12), suggesting that a single gene could be involved in all of these cancers. A significant fraction (56%) of prostate cancer shows LOH at 16q22 in a region telomeric to the *D16S4* marker (5). Although several candidate tumor suppressor genes have been mapped to chromosome 16q22, no definitive data are currently available regarding the possible involvement of these genes in human neoplasia. E-cadherin, a gene normally involved in cell adhesion and mapping within regions of LOH at 16q22, has been suggested to be a tumor suppressor gene (28). Two other genes involved in cell adhesion, M-cadherin (29) and cell adhesion regulator map to 16q24.3 (30), and also represent possible candidates for involvement in tumorigenesis.

The presence of the t(6;16) translocation in the LNCaP cell line and the known involvement of this region in human tumors suggests that the translocation results in distruption of a gene that may be playing an important role in malignant transformation. We decided to identify the genes involved by molecular cloning of the translocation breakpoint. The characterization of this rearrangement and identification of the genes involved represents the first report of a putative chimeric protein which may play a role in prostate carcinogenesis.

Mapping of the breakpoint using rodent-human hybrids carrying the der(6) chromosome involved in the translocation first indicated that the breakpoint on chromosome 16 is located within the *hpr* gene. Southern blotting analysis with *hpr* probes on LNCaP DNA confirmed this finding, indicating the presence of an *hpr* gene rearrangement in this cell line (Fig. 1). Sequence analysis of the cloned breakpoint present in the der(6) chromosome showed that the translocation resulted in fusion of the last intron of the *hpr* gene with the *tpc* gene located on chromosome 6. A complex rearrangement of intronic *hpr* sequences surrounding the breakpoint was found in the LNCaP cell line. The insertion with inversion and deletion, described in the previous section, probably resulted from recombinatorial events associated with the translocation and may have no other physiological significance. Northern blot analysis of LNCaP RNA with a *tpc* probe (B4) indicated the presence of two abnormal transcripts derived from the translocation (Fig. 3). A cDNA clone likely corresponding to the larger transcript was isolated from an LNCaP cDNA library. This clone, named *tpc/hpr*(i) (Figs. 2 and 5), contains all of the *tpc* ORF and part of the *tpc* 3′ untranslated region fused to *hpr* intronic sequences. In fact, the fusion point in the *tpc/hpr*(i) clone is identical to the genomic fusion point from the der(6) chromosome (Fig. 2), indicating that this clone contains intronic sequences that are not spliced out of the mRNA. As mentioned above, *tpc/hpr*(i) contains all of the *tpc* ORF, therefore, this

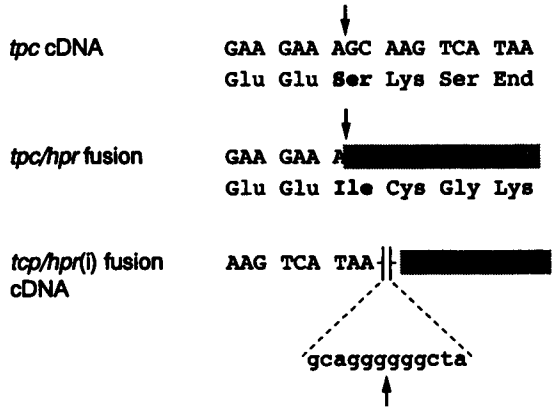

Fig. 5. Sequence of normal and fusion cDNAs surrounding breakpoint regions. Predicted amino acid sequences are depicted beneath the top and middle DNA sequences. *Top sequence*, normal *tpc*; *middle sequence*, *tpc/hpr*; bottom sequence, *tpc/hpr*(i). *Arrows*, breakpoints. *Upper case letters*, coding sequences; *lower case letters*, intronic sequences. *hpr* coding sequences are contained within *gray boxes*. In the case of *tpc/hpr*(i), 12 bp of a total of 1064 bp of the intronic sequence surrounding the breakpoint are depicted below coding sequences retained in the cDNA.

mRNA may result in the synthesis of normal TPC protein and is unlikely to play a role in malignant transformation.

A cDNA clone deriving from the smaller transcript seen by Northern blotting on LNCaP cDNA was cloned by reverse transcription-PCR using primers derived from *tpc* and *hpr* exons present in the genomic fusion depicted in Fig. 2. This cDNA, named *tpc/hpr*, contains an in-frame fusion of *tpc* with *hpr* sequences, with one new amino acid created at the fusion point. This mRNA may thus code for a fusion protein playing a role in tumorigenesis.

HPR is highly homologous to HP, an acute response plasma protein involved in control of the inflammatory response to infection and other pathological states (31). HP expression is known to be restricted mainly to the adult liver; *hpr* RNA, however, has not been detected in any fetal or adult tissues. The presence of HPR sequences in the TPC/HPR fusion protein may result in aberrant localization of TPC, or alternatively, ectopic expression of a part of *hpr*, resulting from the translocation, may contribute to the pathological process. As mentioned previously, the *tpc* gene shows homology to the S10 ribosomal protein, a 30S subunit component, and is therefore likely to play a role in maintainance of ribosome structure. Both ribosomal proteins and proteins involved in ribosomal assembly have been previously implicated in malignant transformation. NPM, a ubiquitously expressed nuclear phosphoprotein involved in ribosomal assembly and nuclear-cytoplasmic transport, is fused to the *alk* gene product, a putative tyrosine kinase receptor, by the t(2;5) translocation associated with malignant lymphomas (32). In addition, mutations in the *Drosophila* homologue of human ribosomal protein RPS6 have been found to cause the appearance of melanotic tumors of the larval lymphoid system (33). It is possible that the transforming potential of fusion proteins containing abnormal ribosomal components, such as NPM/ALK and TPC/HPR, depends in part on interference with the ribosomal function. This may result in abnormal levels of protein translation, and thus indirectly affect cell growth and survival. Indeed, *Drosophila rpS6* has been implicated in egg development, imaginal disk cell survival, and control of hematopoietic differentiation (33, 34), suggesting that alterations of ribosomal protein function may have wide-reaching effects on normal cell function. Thus, although further studies are necessary to determine the significance of the TPC/HPR fusion protein in the development or progression of prostate cancer, it seems likely that the study of this gene fusion may provide important clues to the pathogenesis of this neoplasia.

Acknowledgments

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