Trisomy 7 by Dual-Color Fluorescence in Situ Hybridization: A Potential Biological Marker for Prostate Cancer Progression

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ABSTRACT

Smear preparations from fine-needle aspirates of 30 prostatic carcinomas obtained from radical prostatectomy specimens were examined by a dual-color fluorescence in situ hybridization (FISH) method for the presence of chromosome 7 trisomy (chromosome 9 was used as a control). The frequency of cells with trisomy 7 was determined in tumors and normal prostatic epithelial cells in each specimen. Comparison between the tumor and normal cells from the same patients showed that within all stages, the frequency of trisomy 7/disomy 9 cells in the tumor cells was significantly higher than that observed in the normal cells (P < 0.0001). Furthermore, the mean frequency of cells with trisomy 7/disomy 9 in advanced stages was significantly elevated over the mean frequency observed in organ-confined tumors (P = 0.02). These results are consistent with our previous data on paraffin-embedded prostate tissue sections using single-color FISH procedures. However, the method used in the present study enhances the accuracy of distinguishing trisomic 7 cells from potentially triploid (trisomy 7/trisomy 9) cells. Furthermore, the use of fine-needle aspirates rather than paraffin sections provides an easy method to examine whole nuclei. Our study also suggests that FISH provides a better measure of genetic instability (e.g., aneuploidy) in prostate tumors than flow cytometry.

INTRODUCTION

Prostate cancer is the second leading cause of cancer death among men in the United States. Recent advances in diagnostic tests such as serological tests for prostate-specific antigen, coupled with ultrasound and improved biopsy techniques, have led to early detection of this disease in asymptomatic men. However, early detection creates treatment dilemmas due to a lack of tests that can identify clinically significant tumors. Therefore, there is a need for identification of a biological marker that can distinguish potentially aggressive tumors from biologically indolent tumors. Because the potential of a tumor to become malignant or metastatic is most likely under genetic control, tests that explore the genetic differences of latent and malignant tumors are under intense investigation.

Attempts to find chromosomal abnormalities in prostate cancer by cytogenetic or molecular cytogenetic methods have identified numerous chromosomes that are frequently altered in this cancer. Gains, losses, or structural abnormalities of nearly every chromosome have been observed in various prostate tumors. Among the chromosomes that most frequently show gains are chromosomes 7, 8, and X; those that show frequent losses are chromosomes Y and 10; and those that show common structural abnormalities include chromosomes 1, 4, 5, 7, 8, and 10 (1–16). Trisomy 7 was found to be the only clonal abnormality in one primary prostatic carcinoma (17).

Investigation of genetic changes in prostate cancer by molecular methods has yielded interesting but somewhat confusing results. Allelic losses of various genetic loci have been observed in prostate cancer. These loci are located on several chromosomes, including chromosomes 7q (18), 8p (19, 20), 10q (19, 21), 13q (22), 16q (19, 21), 17 (23, 24), and 18q (25). It is believed that cancer development in the prostate follows a multistage carcinogenesis model in which accumulation of different genetic defects may be responsible for the ability of a tumor to progress from an initiation stage to advanced stages and to become a metastatic cancer (26). This model suggests that allelic losses of chromosomes 8p, 10q, and 16q may be associated with early stages of the tumor, e.g., prostatic intraepithelial neoplasia and histological prostate cancers. As the tumor progresses to a localized clinical cancer, it may accumulate additional genetic changes, such as LOH3 of loci on chromosomes 6q, 7q, 13q (Rb), and 18q. The progression of a localized tumor to a metastatic cancer may involve further genetic changes involving LOH of loci on chromosomes 17p (p53) and 11 and gains of chromosome 7 (trisomy 7) and 8q (MYC amplification).

None of the cytogenetic or genetic markers identified thus far has a proven value for predicting progression or metastasis of prostate cancer. Presently, the most useful clinical parameters for predicting the metastatic potential of prostate cancer are grade, volume, and DNA ploidy of the tumor (27). Although DNA ploidy is currently accepted as the most accurate measure of metastatic potential, it does not categorically predict metastasis (28); metastatic potential is confirmed only by identifying metastases with staging lymphadenectomy. Furthermore, many studies have shown that flow cytometry is not sensitive in detecting chromosomal aneuploidy (10–12). Therefore, a new prognostic genetic marker would be clinically useful and desirable. Such a marker would allow clinicians to use different

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3 The abbreviations used are: LOH, loss of heterozygosity; FISH, fluorescence in situ hybridization; DAPI, 4',6-diamidino-2-phenylindole.
treatment strategies for patients who have different risks of cancer progression.

In a recently published study, we used the technique of single-color FISH to demonstrate that chromosome 7 trisomy is associated with the progression of human prostate cancer (29). Our results showed that the frequency of trisomy 7 cells was significantly increased ($P < 0.05$) in the advanced-stage tumors (stages C and D), but not in the early (stage B) tumors or normal prostatic tissue. Furthermore, metastases were found to have a higher frequency of trisomy 7 cells than primary tumors ($P = 0.005$), whereas chromosome 9, used as an internal control, was predominantly disomic in all primary and metastatic tumors. Most interestingly, in two patients with paired primary and metastatic tumors, trisomy 7 cells increased from 4–7% in the primary tumors to 42–45% in the metastatic tumor cells in the bone marrow. Therefore, these preliminary data suggest that trisomy 7 may be a common feature associated with the local and metastatic progression of human prostate cancer, and it may serve as a novel genetic marker for human prostate cancer progression.

In this report, we describe an improved dual-color FISH assay to determine concomitantly the frequencies of aneuploidy for chromosomes 7 and 9 in the same cells. This modified assay improves the accuracy of distinguishing true trisomy 7 cells from triploid cells. Results of the frequency of trisomy 7 cells in 30 prostate cancers are correlated with DNA ploidy analysis by flow cytometry.

**MATERIALS AND METHODS**

**Clinical Material.** Smears were prepared from fine-needle aspirates obtained from palpable tumors of radical prostatectomy specimens. The smears were air dried and subsequently fixed in 3:1 methanol:acetic acid for 1 min and stained in Hemacolor solutions 2 and 3 for 20 s and 1.5 min, respectively (EM Diagnostic Systems, Gibbstown, NJ). The stained smears were examined with a microscope equipped with a digital X- and Y-axis coordinate locator. Microscopic fields containing prostatic adenocarcinoma cells and normal prostatic epithelial cells were identified according to previously established diagnostic criteria (30) and were recorded separately. Tumor cells were identified by architectural and cytological features, including the presence of three-dimensional cell clusters, acinar formation, nuclear enlargement, hyperchromasia, and prominent nucleoli. Areas of the smear that could not be unequivocally diagnosed as benign or malignant were not included in the cell count. Smears obtained as controls from areas of the prostate without palpable lesions were screened to exclude the presence of carcinoma.

**FISH.** The procedure for dual-color FISH was modified from that described previously (29). Chromosome 7- and 9-specific centromeric DNA probes were obtained from Oncor, Inc. (Gaithersburg, MD). The chromosome 7 probe was biotin labeled, and the chromosome 9 probe was digoxigenin labeled. Chromosome 9 was chosen as an internal control because aneuploidy of this chromosome is uncommon in prostate cancers.

The hybridization procedures followed those described previously (29). The hybridization signals for chromosome 7 were revealed by treating cells with FITC-avidin (green). Chromosome 9 hybridization signals were detected by treating cells with rhodamine-antidigoxigenin (red). The cells were then counterstained with DAPI (0.4 μg/ml), which was dissolved in an antifade solution containing p-phenylenediamine (1 mg/ml), before being examined under a Nikon Microphot-SA fluorescence microscope.

**FISH Analysis and Microscopy.** Previously identified microscopic fields of tumor and normal cells were relocated after FISH and examined for the frequencies of chromosome 7 and 9 aneuploidies. Hybridization signals were enumerated in 400 interphase nuclei/specimen, 200 in tumor areas and 200 in normal areas of the smear. A triple band-pass filter (Omega Optical, Brattleboro, VT) was used to view FITC (green), rhodamine (red), and DAPI (blue) simultaneously. The number of red and green hybridization signals in each cell was recorded. Then the percentage of cells with trisomy 7 was determined by two ways: dual-color and single-color FISH. In dual-color FISH, the percentage of cells with three green and two red signals (three chromosome 7 and two chromosome 9 signals) was determined in each specimen. For single-color FISH, the percentage of cells with three green signals (regardless of the number of red signals) was determined in each sample. Color photographs were obtained with the ProbeMaster image analysis system (Perceptive Scientific Instruments, Inc.).

**Flow Cytometry.** For flow cytometric analysis, fine-needle aspirates (two passes) of the same area of tumor were obtained and transferred to RPMI 1640 (Irvine Scientific, Santa Ana, CA). Samples were washed twice in PBS (Irvine), and the cell count was adjusted to $1.0 \times 10^{6}$ cells/ml. Specimens were analyzed for DNA content using the two-step acridine orange method described previously (31). Briefly, the cell suspension was subjected to detergent treatment at pH 1.2 for 45 s to render cells permeable. Acridine orange was added at a concentration of 5 μg/ml in $5 \times 10^{-3}$ M EDTA, 0.15 mM NaCl, and 0.1 M phosphate-citrate buffer (pH 6.0). Cells were immediately analyzed using an EPICS Profile II cytometer with the standard optical configuration. Doublet discrimination was performed by collecting peak versus integral DNA fluorescence signals. The DNA index was defined using conventional guidelines (32).

**Statistical Analysis.** The Kruskal-Wallis test, a nonparametric equivalent to ANOVA, was used to compare differences among several groups of specimens. If the null hypothesis was rejected (i.e., overall differences were significant), a multiple-comparison procedure was used to determine which pairs of populations tended to differ (33). The Wilcoxon rank sum test was used to test between two groups. Spearman’s rank correlation coefficient was used to determine the degree of correlation between FISH and ploidy.

**RESULTS**

Table 1 shows the pathological stage, Gleason score, ploidy, and frequencies of trisomy 7 cells as determined by single- and dual-color FISH in the tumor and normal cells of 30 prostate cancer smears. Examples of trisomic 7 cells detected by dual-color FISH are shown in Fig. 1. The mean ± SD of the frequencies of trisomy 7/disomy 9 cells in organ-confined tumors (stage B), tumors with extraprostatic extension with or without positive margins (stages C+ and C−), and tumors with...
Table I  Pathological stage, Gleason score, ploidy, and frequency of cells with trisomy 7 as determined by single-color and dual-color FISH in 30 prostate cancer specimens and corresponding normal cells of the same patients

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<th>Tumor</th>
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a  B, tumor confined to prostate; C, extraprostatic extension; seminal vesicle involvement; D1, positive pelvic lymph nodes; −, margin of resection free of tumor; and +, margin of resection involved by tumor.

b  NA, not available; and TFC, too few cells for analysis.

Percentages were observed in normal cells by single- and dual-color FISH. Results of statistical analyses of data obtained by single-color FISH paralleled those of dual-color FISH. For example, by the Kruskal-Wallis test, the overall comparison of means among the three groups showed significant differences ($P = 0.006$). The multiple-comparisons procedure showed that the mean frequency of cells with trisomy 7/disomy 9 in stage C$_v$ and D$_1$ was significantly elevated over the frequency observed in stage B ($P < 0.005$). The difference of stage B versus stages C+/C− and between stages C+/C− and C$_v$/D$_1$ was not significant. Comparison between the tumor and normal cells from the same patients showed that within all stages, the frequency of trisomy 7/disomy 9 cells in the tumor cells was significantly higher than that observed in the normal cells ($P < 0.0001$). A few cells with trisomy 7/disomy 9 were observed among cells interpreted as normal. These cells most likely represent isolated tumor cells admixed with normal cells. This finding was most frequently observed among high-grade tumors (Gleason score ≥8), which exhibited the greatest number of isolated tumor cells.

The percentage of tumor cells with trisomy 7 as determined by single-color FISH was generally greater than that determined by dual-color FISH in most tumor samples. In contrast, similar percentages were observed in normal cells by single- and dual-color FISH. The difference of stage B versus stages C+/C− and between stages C+/C− and C$_v$/D$_1$ was not significant. The difference of stage B versus stages C+/C− was not significant, neither was the difference between stages C+/C− and C$_v$/D$_1$. Comparison between tumor and normal cells from the same patients showed that within all stages, the frequency of trisomy 7 cells in the tumor areas was significantly higher than that observed in the normal cells ($P < 0.0001$).

To compare the frequency of trisomy 7 cells in tumors with low versus high Gleason scores, we grouped tumors into two groups: Gleason score 6 and Gleason scores 7–10. The mean frequencies ± SD of trisomy 7 cells (as determined by dual-color FISH) in tumors with a Gleason score of 6 and in tumors with Gleason scores of 7–10 were 5.4 ± 3.6 and 9.86 ± 6.8, respectively. By the Wilcoxon rank sum test, the difference was
Trisomy 7 and Human Prostate Cancer Progression

Fig. 1 Examples of normal prostatic epithelial cells with disomy 7/disomy 9 (left) and tumor cells with trisomy 7/disomy 9 (right) by dual-color FISH. The hybridization signal for chromosome 7 centromeres appears green (FITC), and that for chromosome 9 appears red (rhodamine; see "Materials and Methods"). Cells were counterstained with DAPI (blue). A triple band-pass filter was used to view all three colors simultaneously. A ProbeMaster image analysis system (Perceptive Scientific Instruments, Inc.) was used to produce this photograph.

almost significant ($P = 0.062$). Similar results were obtained by single-color FISH.

Flow cytometric DNA ploidy analyses yielded interpretable histograms in 24 of 30 specimens. DNA diploidy was manifested in 16 (66.6%), and DNA aneuploidy was apparent in 8 (33.4%) specimens. Although all DNA-aneuploid cases showed chromosomal aneuploidy, the majority of DNA-diploid tumors showed similar abnormality. Spearman's rank correlation coefficient was used to determine the relationship between the frequency of trisomy 7 and ploidy levels of the tumors studied. No statistically significant correlation ($r = 0.3$) was observed between FISH and ploidy results.

**DISCUSSION**

This study confirms our earlier findings that chromosome 7 trisomy is associated with progression of human prostate cancer from stage B to stages C, C, and D (29). We believe that the elevated frequency of trisomy 7 cells in advanced tumors reflects genetic instability in these tumors. Genetic instability is manifested frequently by the production of numerical chromosomal aberrations. The gains and losses of certain chromosomes may occur more frequently than others. Our results are consistent with findings of other investigators who have used multiple DNA probes to demonstrate that a gain of chromosome 7 is one of the most frequent chromosomal abnormalities in prostate cancer. Brown et al. (12) showed that 88% of all aneuploid tumors in their study of 40 tumors by 12 probes had gains of chromosomes 7 and 8. Similarly, Visakorpi et al. (11) showed that gains of chromosomes X, 8, and 7 were associated with 94% of all aneuploid cases in their study of 23 tumors by 10 probes. Unfortunately, neither study correlated aneuploidy frequency with the stage or grade of the tumor. In a few studies in which such a correlation was examined, trisomy 7 was consistently found to occur frequently in advanced cancers. For example, studies by Takahashi et al. (13) showed that gains of chromosomes 7 and 8 were strongly associated with higher Gleason scores (greater than 8), with $P < 0.0001$ and $P < 0.01$, respectively. Furthermore, a study by Zitzelsberger et al. (14) also showed that numerical aberration of chromosome 7 was present in 78% of advanced tumors. The clinical significance of trisomy 7 in prostate cancer has been best demonstrated by Alcaraz et al. (15), who showed that chromosome 7 was the single chromosome most significantly and nonrandomly associated with prostate tumors from patients with a poor prognosis.

The biological significance of trisomy 7 in prostate cancer progression is unclear. However, chromosome 7 is known to contain an oncogene, c-erbB (epidermal growth factor receptor gene), the increased expression of which has been associated with advanced stage, recurrence, and poor prognosis and survival of several types of cancer (34–36). Additionally, a putative prostate tumor suppressor gene has been shown to reside on chromosome 7q31 (18). Frequent LOH at this locus has been shown to be associated with prostate tumor progression (37). Furthermore, human chromosome 7 has been shown to be the only human chromosome that is necessary and sufficient for both the establishment and maintenance of invasiveness and metastatic potential in interspecies T-cell hybrids (38). Therefore, these data taken together suggest that genomic imbalances resulting from trisomy 7 contribute to genetic instability and tumor progression in prostate cancer.

Most investigators, including us, used single-color FISH in previous studies to detect aneuploidy in prostate cancer. By this method, cells with trisomy 7 could not be distinguished from triploid cells (i.e., every chromosome is present in three copies). However, the significance of trisomy 7 cells could be very different from that of triploid cells. Therefore, to determine the
extent of potential triploidy, we performed a dual-color FISH procedure on prostate tumor specimens. In this procedure, chromosome 7 was labeled green, and chromosome 9 was labeled red. Therefore, the copy numbers of chromosomes 7 and 9 could be simultaneously determined in the same cell. Cells that exhibited three green hybridization signals and two red signals were most likely true trisomy 7 cells and not triploid cells. Indeed, the frequency of trisomy 7 cells identified by single-color FISH was higher than that identified by dual-color FISH in most samples studied, suggesting the presence of triploid cells in most tumors. The frequency of triploid cells varied greatly from tumor to tumor. As can be seen in Table 1, in some tumors (patients 3, 10, and 11), only about one-half of the trisomy 7 cells identified by single-color FISH may be true trisomy 7 cells. Whereas in others (patients 1, 4, 5, and 16), nearly all of the trisomy 7 cells identified by single-color FISH are likely true trisomic 7 cells. Normal cells did not appear to contain triploid cells in the specimens studied. Despite the lower frequency of trisomic 7 cells detected by the dual-color FISH method, data from this study do confirm our earlier findings using the single-color FISH method that the frequency of trisomy 7 cells is significantly elevated in advanced stages (Cv and Dv) of prostate cancer. It is interesting to note that stage B tumors of several patients (e.g., patients 6, 11, 12, 15, and 17) showed relatively high frequencies of trisomic 7 cells. Longer follow-up is necessary to determine whether these patients have a worse prognosis or shortened survival.

The lack of statistically significant correlation between the frequency of aneuploidy determined by FISH and ploidy levels determined by flow cytometry is not unexpected. Several previous studies have shown that FISH is more sensitive than flow cytometry in detecting aneuploidy in prostate tumors (10–12). Therefore, we believe that FISH will provide a better measure of genetic instability in prostate tumors than will flow cytometry. The presence of trisomy 7 in aneuploid tumors with diploid ploidy also suggests a possible association of this chromosome in early tumor progression.

The consistent finding of trisomy 7 in advanced stages of prostate cancers by us and others indicates that this abnormality may be a useful biological marker for prostate cancer progression. The dual-color FISH method used in the present study increases the accuracy of identifying true trisomic 7 cells. Additionally, our ability to fine tune the FISH method in smear preparations of fine-needle aspirates, rather than in the paraffin-embedded tissue sections, provides an easy method to examine whole nuclei. If our finding is confirmed in a large-scale study, this marker may be useful for future treatment planning based on patients’ risks of cancer progression.

REFERENCES

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