EXPRESSION OF MAJOR GENE REARRANGEMENT IS FOUND IN PATIENTS WITHPROSTATE CANCER HCFMRP

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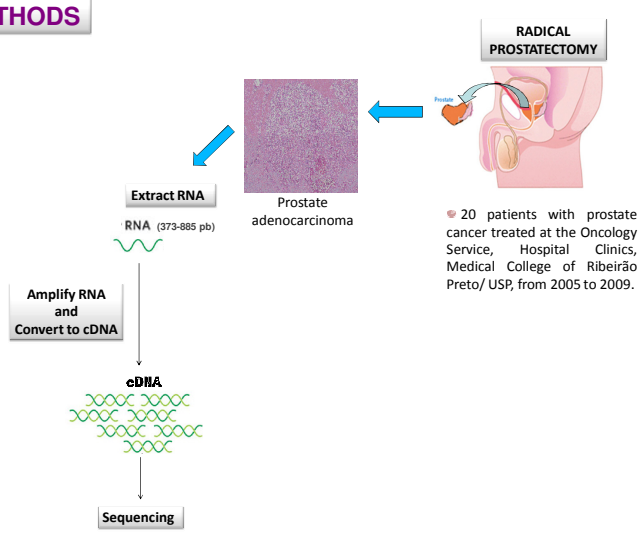
INTRODUCTION

Clinically there are two groups of prostate cancer: one that remains confined to the prostate, relatively indolent, and metastatic and other that eventually culminates in death. Emerging data confirm that recurrent chromosomal rearrangements may be driven by nuclear transcription factors such as the ligand-bound androgen receptor in prostate cancer. Half of prostate cancers harbor gene fusions between androgen-regulated genes TMPRSS2 and members of the ETS transcription factor family.. African-American, Caucasian, and Oriental populations have this fusion in a frequency ranging from 40 to 70%, and some had their isoforms (fig.1) associated with increased aggressiveness of the tumor (higher Gleason score, early recurrence of PSA, and seminal vesicle invasion). Given the high incidence of PCa in Brazil and in view of its population diversity would be extremely important to know the prevalence and level of expression this rearrangement in this population.

METHODS



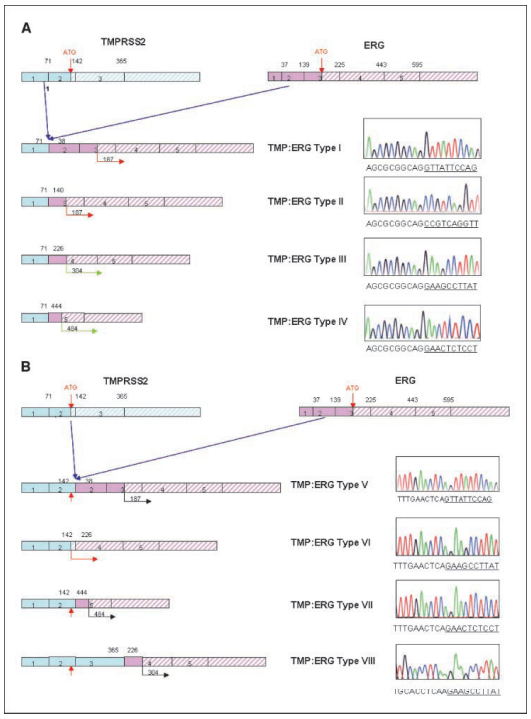


Figure 1. TMPRSS2/ERG fusions mRNAs in prostate cancer. A, schematic structure of TMPRSS2/ERG fusion mRNAs types I to IV. Exons (boxes) for TMPRSS2 (blue) and ERG (purple) are numbered according to Genbank reference sequences (NM_005656 and NM_004449). Numbers above the exons, last base of each exon; vertical red arrow, native ATG; hatch marks, longest open reading frame. For each type of fusion, numbers above the fusion site are the last base pair in TMPRSS2 and the first base pair in ERG gene. Insets, position and automated DNA sequencing of the fusion sites, with the ERG sequence underlined. Horizontal arrow, first in-frame translation initiation site; its location in the ERG gene is shown. Red, translations from native ATGs; green, translations from nonnative ATGs. B, schematic structure of TMPRSS2/ERG fusion mRNAs types V to VIII. Fusion mRNAs are illustrated as described above. Red vertical arrows, position of the out-of-frame native TMPRSS2 ATG; black horizontal arrow, first in-frame ATG in the ERG gene; horizontal red arrow, TMPRSS2/ERG fusion protein initiation site in the type VI mRNA (Wang, J. *et al.* 2006).

RESULTS AND DISCUSSION

Of the total 20 patients assessed, the fusion was present in 35% of cases (Fig. 2), all belonging to type III fusion mRNA (Fig. 3).

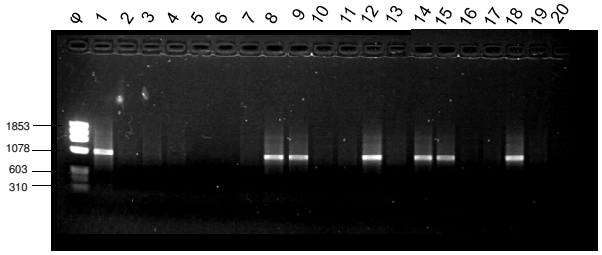


Figure 2. RT-PCR amplification of TMPRSS2/ERG fusion transcripts in prostate cancer. No 01, 08, 09, 12, 14, 15 and 18 are representative for single fusion RT-PCR products type III.

This finding is in agreement with previous studies performed in other populations that found this class of fusion in a greater percentage of cases. This isoform expressed a hybrid protein predicted to be shorter than the protein ERG not fused by 39 aminoacids residues. It occurs because this isorform contains the translation initiation in an internal non-native ATG codon of the gene ERG.

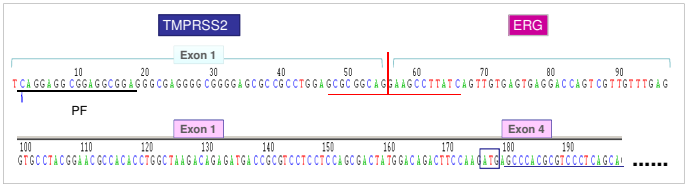


Figure 3 - Schematic representation of the sequence of the gene rearrangement TMPRSS2/ERG belonging to type III isoform. Shows the region which binds the primer, represented by the black line, and the region of fusion between exon 1 of TMPRSS2 and ERG exon 4, represented by the line in red. Blue boxe, internal ATG; blue line first in-frame ATG in the ERG gene. Suspension points continuation of exons of the gene ERG isoform present in type III.

Thus, these proteins have a reduced or modified biological activity, which is associated with a less aggressive tumor phenotype than other isoforms, such as type I, II and VI, which contains a native gene ERG ATG start codon (Fig.3). The analysis of the remaining patients and the level of expression of these isoforms by RT-PCR is the next stage of the project seeking more knowledge that supports the hipothesis of correlation between the isoforms of fusion TMPRSS2/ERG with clinical aggressiveness of prostate cancer and its prevalence.

Conclusion

So far there is a interesting frequency of rearrangement in the study population, indicating that early detection of these rearrangements in admixed populations such as Brazilian population is a good prediction of the prognosis of PCa that can be extremely useful in the clinical management of these patients.

SUPPORTED BY

CAPES