ID: 00954
Type: Oral Comunication
Topic: Tumor biology

High ETV1 levels are associated with shorter PSA-progression time in prostate cancer, but ETS overexpression is lower in GG5 tumors.

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Introduction

Mutations in classic oncogenes and tumor suppressor genes are relatively uncommon in prostate carcinoma (PrCa). Conversely, it is well known that *ERG* is an *ETS*-family member overexpressed in most of the *TMPRSS2-ERG* rearranged prostate tumors (PrCa) and that *PTEN* loss is often a concomitant late event that cooperates with *ERG* overexpression to promote tumor progression. Seven PrCa subtypes defined either by *ETS* fusions or by mutations in driver genes were established by the Cancer Genome Atlas project (TCGA). There is a remarkable molecular diversity among the *ETS*-fused tumors, because overexpression of other *ETS* members (*ETV1*, *ETV4,* and *ETV5*), has been reported to be involved in prostatic carcinogenesis, mostly in tumor invasion and metastasis. However, there is little information on the role of the non-*ERG ETS* genes (*ETV1, ETV4,* and *ETV5*) in the pathogenesis of prostate cancer.

Objectives

The aim of the present study has been to investigate the impact of *ETV1*, *ETV4,* and *ETV5* in prostatic carcinogenesis and their association with *ERG* overexpression and *PTEN* loss, as well as with pathological features and PSA progression-free survival.

Methodology

ETS genes (ERG, ETV1, ETV4 and ETV5) expression levels were analyzed from RNA by RT-qPCR in 104 PrCa (PSMAR-Biobank, Barcelona, Spain) using TaqMan® Gene Expression Assay probes and primer mix (Applied Biosystems, Life Technologies Corporation, CA, USA). *GAPDH* gene was used as internal control to normalize levels of mRNA expression. The 3 non-tumor samples were used to determine normal expression levels of *ERG*, *ETV1*, *ETV4,* and *ETV5* applying the 2^(-ΔΔCt). In addition, protein expression of ETV1, ERG, and PTEN was analyzed by immunohistochemistry thought TMA in an independent cohort of 194 PrCa (PSMAR-Biobank, Barcelona, Spain). According to the Grade Group (GG) classification proposed by the WHO-ISUP 2016, tumor samples were classified from less to more aggressive as: GG1, GG2, GG3, GG4, and GG5. Fisher or Chi-square tests were used to compare categorical variables between groups. PSA progression-free survival was analyzed using Kaplan-Meier (Long-Rank) test.

Results

ETS gene overexpression was found in 68.3% cases, being *ERG* the most frequently overexpressed, followed by *ETV1* (18.3%), *ETV4* (8.6%), and *ETV5* (2.8%). Overexpression of *ETV1*, *ETV4* and/or *ETV5* in absence of *ERG* overexpression was found in 14.4% of tumors. *ERG* showed a trend to be overexpressed as an isolated event (P=0.067). Multiple *ETS* gene overexpression was absent in GG5, while it was seen in 15.4% (4 of 26) GG1, 12.1% (4 of 33) GG2, 9.5% (2 of 21) GG3, and 23.1% (3 of 13) GG4. Compared with the rest of the grade groups, the lack of *ETS* gene overexpression was significantly more common in GG5 (7 of 11; 63.6%) (P=0.034) than in the groups GG1-GG4 taken together (26 of 93; 27.9%) (P=0.034). Finally, there was a trend for GG5 tumors (3 of 11, 27.3%) to have a lower incidence of *ERG* overexpression, compared to GG1-GG4 ones (53 of 93; 56.9%) (P=0.061).

In the TMA analysis, 59 (30.4%) cases overexpressed ETV1 protein, and 91 (46.9%) overexpressed ERG protein. ERG protein overexpression was not associated with ETV1 protein overexpression (P=0.678). PTEN expression loss was statistically associated with ERG overexpression (P=0.006), but not with ETV1 overexpression (P=0.285). ETV1 protein overexpression was statistically associated with GG3-4 tumors (43.1%), compared to GG1-2 (27.9%), and GG5 (20.5%) ones (P=0.049). ERG overexpression was not associated with the grade group classification (P=0.218).

Finally, patients with *ETS* gene overexpression showed a trend to have a shorter time to PSA progression compared to patients with a *wt* phenotype (P=0.078). Moreover, very high levels of ETV1 immunohistochemical expression (histoscore > 177) were significantly associated with a shorter time to PSA progression (P = 0.002).

Conclusions

- *ETS* gene overexpression is a very frequent event in prostate cancer, mostly related to *ERG* but also with a remarkable involvement of other *ETS* genes.

- ETV1 is significantly overexpressed in GG3 and 4 at the protein level.

- Strong intensity of ETV1 protein overexpression seems to be related to worse prognosis.

- GG5 tumors seem to be associated with a lack of *ETS* mRNA overexpression, and it could represent a different PrCa subset, that may evolve trough pathways not related to ETS overexpression.

Support Grants: (FIS/ Carlos III/ FEDER/ PI15/00452, Spanish Ministry of Health).

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