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Prognostic potential of ERG (ETS-related gene) expression in prostatic adenocarcinoma

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Abstract

Purpose—Following patients after prostatectomy can be expensive and stressful, therefore, a novel and reliable approach to improve stratification is needed both at diagnosis of PCa and following its treatment. We evaluate the association of both ERG and claudin-4, -5 and betacatenin expression in tumor tissues of patients with organ confined and advanced prostatic adenocarcinomas.

Methods—A total of 30 patients were included in the study. Nine men, who underwent radical prostatectomy for organ confined (pT2N0M0) cancer (OCC); 11 patients with clinically advanced cancer (CAC); and 11 controls with benign prostatic hypertrophy (BPH). Using immunohistochemistry applied to tissue microarrays, each group was evaluated for beta-catenin, claudin-4, -5 and ERG expression.

Results—The expression of ERG was higher in the CAC group as compared to OCC and BPH ($p = 0.7684$, $p = 0.0224$, respectively). Among these patients, 5 from the CAC (45%) and 5 from the OCC group (56%) stained positively for ERG ($p = 1.0$). The mean staining score for those with ERG+ advanced cancer was greater than that for the ERG+ organ-confined cancer ($p = 0.0209$). ERG staining correlated with Gleason score (Pearson correlation: 0.498, $p = 0.0051$), but not with serum PSA level (Pearson correlation: 0.404, $p = 0.1202$). When analyzing outcome data high ERG expressing tumors have shown a significantly worse overall survival ($p = 0.0084$).

Conclusions—Our results of presence or absence of claudin-4 and -5 and ERG staining intensities suggest their potential as prognostic factors for prostate cancer.

Keywords

prostate; prognosis; prediction; ERG; claudin

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Introduction

Since the introduction of prostate-specific antigen (PSA) in the late 1980s, both the number of prostate biopsies performed and incidence of prostate cancer has risen [1,2]. Screening for PCa with PSA, though, is controversial. Some opinion leaders have questioned the role of PSA as a screening tool altogether, advocating that its worldwide use has led to increase in unnecessary biopsies, over-diagnosis of low-grade, low-stage tumors with subsequent over-treatment, without having a considerable impact on prostate cancer-related survival [3–7]. Additionally, control of cancer following prostatectomy in the PSA era has improved [8,9], although it is difficult to predict just who will recur [10]. Continually following patients after prostatectomy can be expensive and stressful [11–13]. Therefore, a novel and reliable approach to improve stratification is needed both at diagnosis of PCa and following its treatment.

In a clinically asymptomatic and normal man the key question to be answered is not only whether he has a cancer but also it is dangerous or not. To improve the specificity of total PSA, which is unfortunately expressed at similar level in benign and cancerous cells, several approaches based on PSA derivatives have been investigated. However, none of these alone have reached a significant improvement in PCa detection. Many prospective new biomarkers have been identified and are currently under investigation, with some showing substantial promise, like PCa biomarkers. Furthermore, the final aim of this study is to find prognostic markers for prostate cancer patients to improve their stratification for outcome and possibly, treatment options.

In general, a good biomarker has to be over-expressed only in prostate cancer cells and ideally should be reproducible, cost effective and also should be correlated with disease outcome. In these settings the future of cancer prognosis might rely on small panels of markers that can precisely predict PCa presence, stage, metastasis, and serve as prognostic factors and substitute end points of disease progression and response to therapy.

The potential of claudins, small tight junction proteins that are involved in intercellular architecture and communication was examined [14–16], both diagnostic and prognostic marker in PCa. Our results suggested that patients with organ-confined (OCC) and advanced cancer (CAC) were subsets with distinct claudin expression profiles, specifically, claudin-4 and -5 was expressed at higher levels in PCa with poor prognosis [17]. Elevated membranous claudin-4 expression was described by others as well to be a marker of poor prognosis in prostate cancer [18].

The *ETS-Related Gene (ERG)* is an oncogene that is over-expressed in PCa when a fusion event places it downstream of the androgen-dependent *TMPRSS-2* promoter normally present 3 mB upstream [19]. Present in 50–70% of PCa patients in Western populations, the *ERG-TMPRSS2* fusion is one of the most common genetic alterations in PCa [20–23]. Furusato et al. recently described a highly specific antibody able to detect the ERG oncoprotein expression with high concordance to genomic rearrangement [24]. In the present study, we evaluate the association of both ERG and claudin-4, -5 and beta-catenin expression in tumor tissues of patients with organ confined and advanced prostatic adenocarcinomas.

Materials and Methods

Patient samples

A total of 30 patients were included in the study (Table 1). Nine men, who underwent radical prostatectomy for organ confined (pT2N0M0) cancer (OCC); 11 patients with

clinically advanced cancer (CAC); and 11 controls with benign prostatic hypertrophy following transurethral resection of the prostate (BPH). Tissue microarrays were used to evaluate the samples of the patients making it feasible to compare the same size of tissue areas in each case: two 2 mm wide cores were taken from each formalin-fixed and paraffin-embedded block for further immunohistochemical analysis.

Immunohistochemistry

Using immunohistochemistry applied to tissue microarrays, each group was evaluated for beta-catenin, claudin-4, -5 and ERG expression. After deparaffination, the slides were treated in pH9 Target Retrieval Solution (#S2368, DAKO, Carpinteria, CA, USA) in a microwave oven for 28 minutes, subsequently, incubation of the slides with primary antibody of ERG-Mab (Clone 9FY, dilution: 1:60, CPDR, Uniformed Services University, Bethesda, MD, USA; now available from Biocare Medical, Concord, CA, USA) diluted in Antibody Diluent (#251018; Ventana Medical Systems, Inc., Tucson, AZ, USA) was performed for 60 minutes at room temperature. The reactions were visualized with UltraView DAB Detection kit according to the manufacturer's protocol (#760-500; Roche Diagnostics, Mannheim, Germany). ERG staining has shown a nuclear expression pattern.

Beta-catenin, claudin-4 and -5 staining were performed for an earlier study [17], where the expression was evaluated in an automated manner. Here, these membranous reactions were re-evaluated semi-quantitatively integrating intensity (0–3) and frequency (0–100) of staining on a scale of 0–300 [25].

Statistics

The analysis was performed with SPSS 17.0 (SPSS, Inc., Chicago, IL, USA). Kaplan-Meier curves were used to plot the efficiency of the prediction on overall survival. Chi-squared test was performed to test relation of ERG and clinicopathological variables grouped into categorical variables. Continuous variables were compared with ANOVA test, and individual groups were tested with post-hoc analysis according to Tukey. Statistically significant results were accepted at p-values of 0.05.

Results

There were 10 patients with clinically advanced prostate cancer and 9 patients with organ confined prostate cancer compared to 11 BPH patients (Table 1).

The expression of ERG was higher in the CAC group as compared to OCC and BPH ($p = 0.7684$, $p = 0.0224$, respectively; Figure 1). Among these patients, 5 from the CAC (45%) and 5 from the OCC group (56%) stained positively for ERG ($p = 1.0$). The mean staining score for those with ERG+ advanced cancer was 270, which was significantly greater than that for the ERG+ organ-confined cancer (158; $p = 0.0209$). ERG staining correlated with Gleason score (Pearson correlation: 0.498, $p = 0.0051$), but not with serum PSA level (Pearson correlation: 0.404, $p = 0.1202$).

Difference was found between the three groups regarding claudin-4 ($p=1.247e-10$) and claudin-5 ($p = 0.0001$) expression regardless of age, PSA level, prostate volume and Gleason score. Claudin-4 and ERG were specifically present in the OCC and CAC, while claudin-5 was strongly expressed in BPH. All BPH specimens were negative for ERG. Expression of ERG did not correlate with expression of claudin-4 or beta-catenin ($p = 0.9764$, $p = 0.8706$, respectively). Claudin-5 has shown a significant correlation with ERG staining (Pearson correlation: -0.477, $p = 0.0246$).

When analyzing outcome data high ERG expressing tumors have shown a significantly worse overall survival ($p = 0.0084$; Figure 2).

Discussion

The potential role of claudins as potential markers of PCa prognosis has been reported previously [17]. We undertook a comparative approach to examine the prognostic potential of ERG in Central Eastern European patients in this pilot study, as claudin-4 has already been established as prognostic marker and the number of herein investigated samples is limited.

In the presented data, there was no statistically significant difference in ERG positivity rates between the organ-confined and advanced prostate cancers. Additionally, although the sample size was limited to this exploratory cohort, the rate of ERG positivity matches those previously reported for Western populations [20–22,19,23].

The expression of the *ERG* oncogene has been extensively studied as a prognostic marker, with inconsistent results[26]. Carefully designed multi-center studied with defined patients cohorts are needed to sort out these apparent differences. With the knowledge that the genomic rearrangement that places the *TMPRSS2* promoter immediately upstream from the *ERG* oncogene can occur by the oncogene's 5' region or its insertion elsewhere, Attard et al. and Mehra et al. explored the prognostic significance of the mechanism of fusion. They determined that the deletion event conveys a poorer prognosis [27,28]. However, other studies suggested that ERG fusion of deletion type is the consequence of aneuploidy [29]. Hu et al. identified two splice variants of the *ERG* RNA: Type I, which codes for the full length ERG protein and type II, which codes for a truncated protein. A high type I to type II ratio, when quantitatively measured, was associated with PSA recurrence [30]. Overall prognostic utility of ERG fusions is uncertain and warrants further investigations [31].

To our knowledge, this is the first study to identify a correlation between intensity of ERG oncoprotein and PCa prognosis. Van Leenders et al. previously noted a correlation between strength of ERG IHC signaling and copies of *ERG* mRNA in prostate cancer cells. They found a statistically significantly higher amount of *ERG* mRNA in those cancer that expressed strong (3+) IHC signals compared to those that had moderate (2+) signaling, but no significant difference in quantitative mRNA levels between those cells with moderate and weak (1+) IHC signals. Contrary to the present results, in a set of 17 patients, they noted no correlation between ERG IHC intensity or mRNA levels with clinicopathological parameters at radical prostatectomy [32]. This study also reported the sensitivity, specificity, positive predictive value and negative predictive value of a positive ERG stain in biopsy was 61%, 94%, 92% and 72%, respectively [32]. Two other groups further explored the applicability of staining biopsy cores with ERG. Yaskiv et al. also sought to explore the diagnostic utility of ERG IHC, but they combined it with the basal cell marker p63, the loss of which is a very sensitive marker of prostate cancer. Because of the specificity of ERG staining, they concluded that $ERG^{+}/p63^{-}$ cores should be diagnosed as prostate cancer [33].

Emerging studies underscore the robustness and ease of ERG IHC in biopsy and prostatectomy specimens, as well as the strong concordance of ERG protein expression in with ERG rearrangements in PCa [34]. These practical solutions are necessary if promising PCa biomarkers, such as claudin, beta-catenin and ERG are to be evaluated to help stratify patients prior to prostatectomy. Recent evidence also suggests that taxanes have a significant impact on androgen receptor signaling [35,36], thus, studies to evaluate the efficacy of taxanes guided by ERG status are of particular interest [37]. This proof of principle study

provides new opportunities in further evaluations of prognostic and predictive utility of quantitative evaluation of ERG in PCa.

Conclusions

In this pilot study, the expression of ERG was higher in the CAC group as compared to OCC and BPH. ERG staining correlated with Gleason score, but not with serum PSA level. All BPH specimina were negative for ERG. When analyzing outcome data high ERG expressing tumors have shown a significantly worse overall survival. Claudin-4 and ERG were specifically present in the pCa groups, while claudin-5 was strongly expressed in BPH. Expression of ERG did not correlate with expression of claudin-4 or beta-catenin, but claudin-5 has shown a significant inverse correlation with ERG. Our results of presence or absence of claudin-4/5 and ERG staining intensities suggest their potential as prognostic factors for prostate cancer, which warrant further investigations in larger series of Central Eastern European population including biopsy samples and prostatectomy specimen comparisons.

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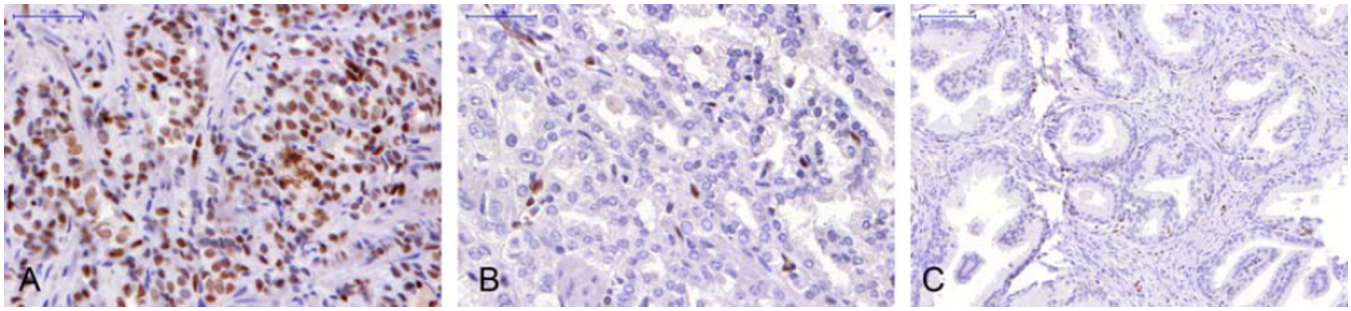

Figure 1.
Immunohistochemical images of ERG expression in advanced (A) and organ confined (B) tumors and benign hyperplastic (C) prostatic tissues (40×).

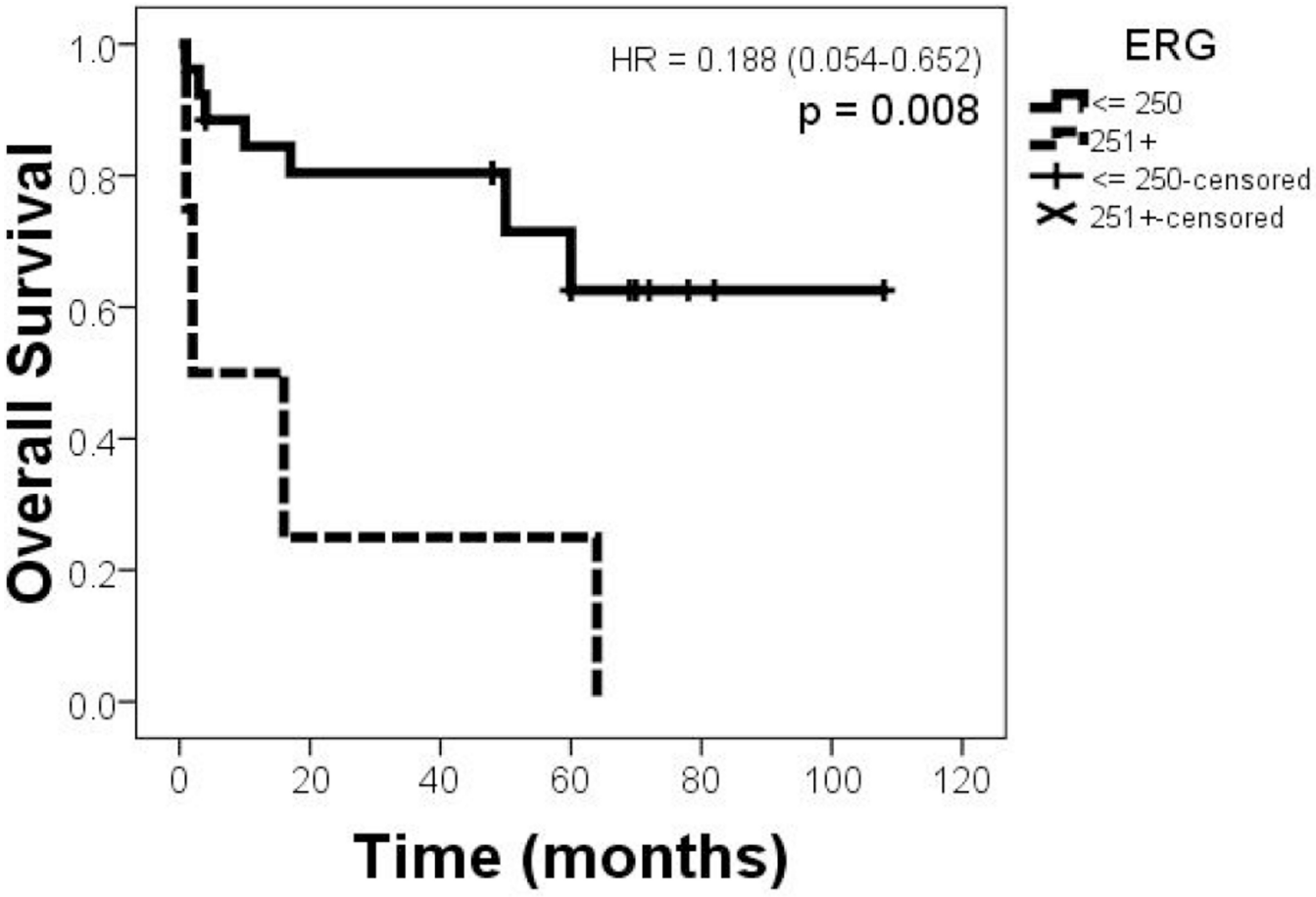

Figure 2.
Kaplan-Meier graph showing the survival curves of the groups based on lower vs. higher ERG expression (binned: 0-250 and 251-300).

Table 1

Clinicopathological and immunohistochemical evaluation of the patients and respective tumors in the study.

GROUP	CAC (n=10)		OCC (n=9)		BPH (n=11)		Sign.
	Mean	***SE***	***Mean***	***SE***	***Mean***	***SE***	
Age	70.09	2.80	62.13	2.29	67.82	0.99	0.055
PSA (serum)	703.45	254.87	22.76	12.12	11.92	2.23	0.001
P.vol (ml)	61.36	9.16	65.24	6.33	88.86	4.56	0.038
Gleason score	7.80	0.42	4.89	0.42	NA	NA	0.001
Beta-catenin	205.00	26.38	91.67	27.84	260.91	26.30	0.001
Claudin-4	258.18	13.06	2.22	2.22	189.09	24.06	0.001
Claudin-5	33.33	33.33	67.78	21.91	226.36	24.73	0.001
ERG	122.73	43.23	90.00	35.91	0.00	0.00	0.025

P.vol - Prostate volume

SE - Standard Error of Mean