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Overexpression of the A Disintegrin and Metalloproteinase ADAM15 is linked to a Small but Highly Aggressive Subset of Prostate Cancers[1]

Christoph Burdelski[*,†,2], Michael Fitzner[*,2], Claudia Hube-Magg[*], Martina Kluth[*], Asmus Heumann[*,†], Ronald Simon[*], Till Krech[*], Till Clauditz[*], Franziska Büscheck[*], Stefan Steurer[*], Corinna Wittmer[*], Andrea Hinsch[*], Andreas M. Luebke[*], Frank Jacobsen[*], Sarah Minner[*], Maria Christina Tsourlakis[*], Burkhard Beyer[‡], Thomas Steuber[‡], Imke Thederan[‡], Guido Sauter[*], Jakob Izbicki[†], Thorsten Schlomm[‡,§] and Waldemar Wilczak[*]

[*]Institute of Pathology, University Medical Center Hamburg-Eppendorf, Germany; [†]General, Visceral and Thoracic Surgery Department and Clinic, University Medical Center Hamburg-Eppendorf, Germany; [‡]Martini-Clinic, Prostate Cancer Center, University Medical Center Hamburg-Eppendorf, Germany; [§]Department of Urology, Section for translational Prostate Cancer Research, University Medical Center Hamburg-Eppendorf, Germany

Abstract

The A Disintegrin and Metalloproteinase (ADAM) family of endopeptidases plays a role in many solid cancers and includes promising targets for anticancer therapies. Deregulation of ADAM15 has been linked to tumor aggressiveness and cell line studies suggest that ADAM15 overexpression may also be implicated in prostate cancer. To evaluate the impact of ADAM15 expression and its relationship with key genomic alterations, a tissue microarray containing 12,427 prostate cancers was analyzed by immunohistochemistry. ADAM15 expression was compared to phenotype, prognosis and molecular features including *TMPRSS2:ERG* fusion and frequent deletions involving *PTEN*, 3p, 5q and 6q. Normal prostate epithelium did not show ADAM15 staining. In prostate cancers, negative, weak, moderate, and strong ADAM15 staining was found in 87.7%, 3.7%, 5.6%, and 3.0% of 9826 interpretable tumors. Strong ADAM15 staining was linked to high Gleason grade, advanced pathological tumor stage, positive nodal stage and resection margin. ADAM15 overexpression was also associated with *TMPRSS2:ERG* fusions and PTEN deletions ($P < .0001$) but unrelated to deletions of 3p, 5q and 6q. In univariate analysis, high ADAM15 expression was strongly linked to PSA recurrence ($P < .0001$). However, in multivariate analyses this association was only maintained if the analysis was limited to preoperatively available parameters in ERG-negative cancers. The results of our study demonstrate that ADAM15 is strongly up regulated in a small but highly aggressive fraction of prostate cancers. In these tumors, ADAM15 may represent a suitable drug target. In a preoperative scenario, ADAM15 expression measurement may assist prognosis assessment, either alone or in combination with other markers.

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Abbreviations: ADAM, a disintegrin and metalloproteinase; CHD1, chromodomain-helicase-DNA-binding protein 1; ERG, erythroblast transformation-specific (ETS) related gene; ETS, erythroblast transformation-specific; FISH, fluorescence in situ hybridization; FOXP1, forkhead box protein P1; MAP3K7, mitogen-activated protein kinase kinase kinase 7; MMP, matrix metalloproteinase; PSA, prostate specific antigen; PTEN, phosphatase and tensin homolog; TMA, tissue microarray; TMPRSS2, transmembrane protease, serine 2

Address all correspondence to: Dr. Ronald Simon, Institute of Pathology, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany.
E-mail: r.simon@uke.de

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[2] These authors contributed equally to this work.

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Introduction

Prostate cancer is the most prevalent cancer in men in Western societies [1]. Although the majority of prostate cancers behave in an indolent manner, a small subset is highly aggressive and requires extensive treatment [2,3]. Established preoperative prognostic parameters are limited to Gleason grade and tumor extent on biopsies, prostate-specific antigen (PSA), and clinical stage. These data are statistically powerful, but often insufficient for optimal individual treatment decisions. It is thus hoped that a better understanding of disease biology will eventually lead to the identification of clinically applicable molecular markers that enable a more reliable prediction of prostate cancer aggressiveness.

The human A Disintegrin and Metalloproteinase 15 (ADAM15) is one of more than 20 members of the ADAM family of type I multi-domain transmembrane glycoproteins that function as zinc-dependent endopeptidases (reviewed in [4,5]). Activated ADAM15 is involved in proteolytic processing of cytokines, growth factors and adhesions molecules [5]. ADAM15 promotes cancer progression in gastric [6,7], lung [8,9] and colon cancers [10] as well as melanomas [11]. It is believed that the tumor promoting action of ADAM15 results from disruption of cell–cell [4,12] and cell-matrix [12] adhesion and from release of membrane-bound growth factors (reviewed in [13,14]). Accordingly, ADAM15 deregulation has been linked to poor patient outcome in lung and colon cancers [9,10]. There is accumulating evidence that ADAM15 may also plays a role for prostate cancer biology. Functional studies in PC-3 prostate cancer cells suggest a role of ADAM15 for metastasis, as the capability to migrate through vascular endothelial cells depends on ADAM15 expression [14]. Moreover, a study on 167 clinical prostate cancer specimens suggested a link between ADAM15 overexpression, metastatic phenotype and poor patient prognosis [15].

These promising findings encouraged us to study the putative prognostic value of ADAM15 expression in a large cohort including more than 12,000 prostate cancers that have been assembled in a tissue microarray (TMA) format and for which clinical follow-up data are available.

Table 1. Pathological and Clinical Data of the Arrayed Prostate Cancers

	No. of patients (%)	
	Study cohort on TMA (N = 12,427)	Biochemical relapse among categories
Follow-up (mo)		
n	11,665 (93.9%)	2769 (23.7%)
Mean	48.9	-
Median	36.4	-
Age (y)		
≤50	334 (2.7%)	81 (24.3%)
51–59	3061 (24.8%)	705 (23%)
60–69	7188 (58.2%)	1610 (22.4%)
≥70	1761 (14.3%)	370 (21%)
Pretreatment PSA (ng/ml)		
<4	1585 (12.9%)	242 (15.3%)
4–10	7480 (60.9%)	1355 (18.1%)
10–20	2412 (19.6%)	737 (30.6%)
>20	812 (6.6%)	397 (48.9%)
pT stage (AJCC 2002)		
pT2	8187 (66.2%)	1095 (13.4%)
pT3a	2660 (21.5%)	817 (30.7%)
pT3b	1465 (11.8%)	796 (54.3%)
pT4	63 (0.5%)	51 (81%)
Gleason grade		
≤3 + 3	2848 (22.9%)	234 (8.2%)
3 + 4	6679 (53.8%)	1240 (18.6%)
3 + 4 Tertiary 5	433 (3.5%)	115 (26.6%)
4 + 3	1210 (9.7%)	576 (47.6%)
4 + 3 Tertiary 5	646 (5.2%)	317 (49.1%)
≥4 + 4	596 (4.8%)	348 (58.4%)
pN stage		
pN0	6970 (91%)	1636 (23.5%)
pN+	693 (9%)	393 (56.7%)
Surgical margin		
Negative	9990 (81.9%)	1848 (18.5%)
Positive	2211 (18.1%)	853 (38.6%)

Percentage in the column "Study cohort on TMA" refers to the fraction of samples across each category. Percentage in column "Biochemical relapse among categories" refers to the fraction of samples with biochemical relapse within each parameter in the different categories. NOTE: Numbers do not always add up to 12,427 in the different categories because of cases with missing data. Abbreviation: AJCC, American Joint Committee on Cancer.

Materials and Methods

Patients

Radical prostatectomy specimens were available from 12,427 patients, undergoing surgery between 1992 and 2012 at the Department of Urology and the Martini Clinics at the University Medical Center Hamburg-Eppendorf. Histo-pathological data was retrieved from the patient files, including tumor stage, Gleason grade, nodal stage and stage of the resection margin. In addition to the classical Gleason categories, "quantitative" Gleason grading was performed as described before [16]. In brief, for every prostatectomy specimen, the percentages of Gleason 3, 4, and 5 patterns were estimated in cancerous tissues during the regular process of Gleason grading. Gleason 3 + 4 and 4 + 3 cancers were subdivided according to their percentage of Gleason 4. For practical use, we subdivided the 3 + 4 and 4 + 3 cancers in 8 subgroups: 3 + 4 ≤ 5% Gleason 4, 3 + 4 6–10%, 3 + 4 11–20%, 3 + 4 21–30%, 3 + 4 31–49%, 4 + 3 50–60%, 4 + 3 61–80% and 4 + 3 > 80% Gleason 4. In addition, separate groups were defined by the presence of a tertiary Gleason 5 pattern, including 3 + 4 Tert.5 and 4 + 3 Tert. 5. Follow-up data were available for a total of 12,344 patients with a median follow-up of 36 months (range: 1 to 241 months; Table 1). Prostate specific antigen (PSA) values were measured following surgery and PSA recurrence was defined as a postoperative PSA of 0.2 ng/ml and increasing at first of appearance. All prostate specimens were analyzed according to a standard procedure, including a complete embedding of the entire prostate for histological analysis [17]. The TMA manufacturing process was described earlier in detail [18]. In short, one 0.6 mm core was taken from a representative tissue block from each patient. The tissues were distributed among 27 TMA blocks, each containing 144 to 522 tumor samples. For internal controls, each TMA block also contained various control tissues, including normal prostate tissue. The molecular database attached to this TMA contained results on ERG expression in 10,678 [19], *ERG* break apart FISH analysis in 7099 (expanded from [20]) and deletion status of 5q21 (*CHD1*) in 7932 (expanded from [21]), 6q15 (*MAP3K7*) in 6069 (expanded from [22]), *PTEN* (10q23) in 6704 (expanded from [23]) and 3p13 (*FOXP1*) in 7081 (expanded from [24]) cancers. The usage of archived diagnostic left-over tissues for manufacturing of tissue microarrays and their analysis for research purposes as well as patient data analysis has been approved by local laws (HmbKHG, §12,1) and by the local ethics committee (Ethics commission Hamburg, WF-049/09 and PV3652). All work has been carried out in compliance with the Helsinki Declaration.